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The Internal Secretions in General Practice.

HARROWER

THIRD EDITION

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PRACTICAL ORGANOTHERAPY

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THE INTERNAL SECRETIONS IN GENERAL PRACTICE

BY

HENRY R. HARROWER, M. D., F. R. S. M. (Lond.)

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THIRD EDITION

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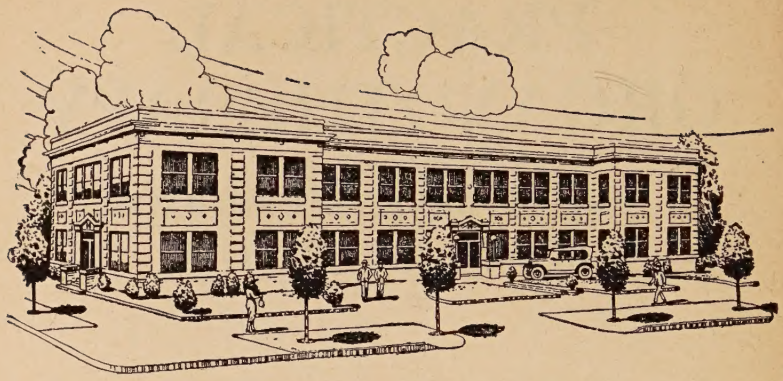
THE HARROWER LABORATORY

GLENDALE, CALIFORNIA



THIS DRAWING illustrates the recently completed Administration Building of The Harrower Laboratory. It houses the general offices, research laboratories, library and translations bureau. The manufacturing departments are in buildings not seen in this view.

Physicians visiting in Southern California are invited to come out to Glendale—the fastest growing residence city (for its size) in the country—eight miles north of Los Los Angeles, and see what we are doing.

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PREFACE TO THE THIRD EDITION

Appreciation must be expressed to many hundreds of physicians who have commented favorably upon the two previous editions of this book. Special thanks are due to many who have "stood up for us", and have labored with the occasional physician who, seeing in my work nothing but a sordid business with its inevitable publicity, have missed the real reason back of the establishment and development of my laboratory, and in their ignorance have criticized my efforts along these lines.

In revising this third edition, I have attempted to make it more valuable, and have added many chapters at the instance of friends who felt that the particular subjects were not given as much consideration as they should have been.

Many of the older chapters have been entirely rewritten, and the new section, "Endocrine Queries and Answers", will, I believe, extend quite considerably the usefulness of this book as a work of reference to those who are interested.

I have not seen fit to prepare bibliographies, but those who are interested in bibliographic confirmation can find a good deal of this in the various issues of *Harrower's Monographs on the Internal Secretions* which is beginning its second year of successful publication, and our librarian will be pleased to assist physicians in gathering bibliographic data on subjects which may be of interest to them.

This third edition, extended not merely as far as contents are concerned, but enlarged in the size of the type and also of the page, bids fair to be a valuable mirror of the work being done by The Harrower Laboratory, and I am making use of this opportunity to express my personal thanks to literally thousands of physicians who have enabled us in the short space of four years to establish a business of very considerable proportions, and to extend the service that we are trying to render to humanity into many homes where, I am glad to say, it has brought much rejoicing.

Henry R. Harrower

Glendale, California,
December 1921.

SECTION I

INTRODUCTION

For more than twelve years I have been studying the glands of internal secretion with increasing interest, and in explanation of the work of a "laboratory of applied endocrinology" now known as "The Harrower Laboratory" which was established in the foothill city of Glendale, eight miles north of Los Angeles, California, in February, 1918, I must preface this book with a few remarks.

The Object of This Book. First of all, let me explain what this book is intended to accomplish and why the previous editions have had so large a distribution (over twenty-two thousand copies were printed *and the printing order for this edition is twenty-five thousand*). As will be quickly seen, I have not been satisfied to take the word of the investigator whose work has been of an experimental character and who says that "the subject is still in its experimental stages," nor of the conservative editor who remarks that "endocrinology and especially organotherapy, is still in a state of chaos," etc. When a hint has come to me I have tried it out, have made it possible for many of my friends and correspondents to apply it *clinically* and, in the course of time, some real information, tested in "the crucible of the clinic," has been developed. I like to say that our work has "*materialized* many ideas pertaining to the internal secretions in general practice;" and to say that many an ephemeral suggestion or half-finished experimental hint has been made tangible and available to thousands of practising physicians, is telling nothing but the truth.

It used to be most aggravating to me to read some interesting article and then learn at its close that "it may be possible, as our knowledge develops, to apply these findings in a clinical way in suitable cases." Now the physician is enabled to apply an idea with no preliminary bother, expense or even trepidation, for, in many instances, at least, this already has been done by hundreds of others.

These prospectively hopeful ideas have been materialized into carefully-worked-out, time-tested pluriglandular formu-

las, and in a generous percentage of the cases in which they have been used—not all by any means, as will be explained in another chapter ("Failures with Organotherapy")—they have rendered a service which has aroused admiration and enthusiasm.

Some Personal History. To revert now, for a few moments, to some reasons for my enthusiasm in this line of study:

My interest in the endocrine glands grew out of some work which I did in 1908-9 on metabolism, acidemia and, especially, the urinary acidity. I wrote a number of papers during that period, some of which appeared in prominent medical journals in America and Europe. In asking myself why faulty metabolism and deficient cell chemistry was brought about I could not but consider the "regulators of metabolism," as Noel Paton calls them—the hormones of the glands of internal secretion.

After several years of casual study in Chicago, I went abroad for more than two years, during which time I had opportunity to visit several of the leading students in this field, in many different countries. My enthusiasm was considerably increased by what I saw and heard, and it was not long before I was convinced that we were far behind our European, and especially our French, colleagues. I have since kept in touch with many of these men, and in 1915-6 succeeded in establishing the *Association for the Study of Internal Secretions,* a body of physicians and investigators whose object is to further and correlate the work of many widely separated students of endocrinology. The Association's bulletin, *Endocrinology,* is a splendid and comprehensive review of the literature and advances in this important study.*

For years I had been impressed with the extreme importance of glandular therapy. I had spent much time and effort to collate data on organotherapy, which was published

* The above Association, now in its fifth year, will welcome cooperation from interested physicians. The present President (Dr. Walter B. Cannon, of Harvard University, Cambridge, Mass.), or Secretary (Dr. F. M. Pottenger, Title Insurance Bldg., Los Angeles), will be pleased to correspond with those who desire to know more about the work and aims of the *A. S. I. S.* While I am not now actively promoting this Association, as its originator and a charter member, I am glad to pass on a word about the excellent service it is rendering to medicine, and especially about the bimonthly journal mentioned above, which is a more than satisfactory return for the annual dues of six dollars.—H. R. H.

in book form—"Practical Hormone Therapy"—in London, in 1914, by Bailliere, Tindall & Cox. Naturally, I found out some of the wonderful things that were being done in the treatment of endocrine disease; and soon found myself wondering why so much attention was paid to obvious thyroid, adrenal, pituitary or gonad disease, when the functions of these glands are of such prime importance to the body that the slightest derangement of their hormone production must in the nature of things exert a more or less decided influence on the body. In other words, I began to see the necessity of studying the minor, functional ductless glandular disorders, and the enthusiasm engendered by the studies has never waned for an instant.

The Relations of the Endocrine Glands. The next logical step was to investigate the effects that certain endocrine dysfunction had on the other internal secretory organs; and it was soon very clear that *to treat a thyroid disorder as such just because it was obviously of thyroid origin was to ignore a fundamental principle which often has resulted in failure.* Let me explain: If a cretin or myxedematous individual really has an insufficient production of the thyroid hormones, and these internal secretions not only regulate many important functions of the body, but also the endocrine function of many or all of the other members of the internal secretory system, how is it possible not to have associated disorders due to the resulting associated dyscrinism?

This means that we must consider the work of the body as a whole—of the endocrine glands as a series, and when we do this we will find that in the hypothyroidism just mentioned there is also a very well defined series of disturbances in the pituitary gland, the sex glands, the adrenals and, in fact, in the whole ductless glandular system. Hence the cretin must have more attention than that given merely to the thyroid insufficiency. *The same applies to every form of dyscrinism.* As has been stated editorially in the *New York Medical Journal* (July 20, 1918): "All [the endocrine glands] are so closely bound to each other that a disturbance in one will throw out of gear or out of action all of the others. . . . It is for this reason that in conditions thought to have origin in this form of disturbance gland medication, organotherapy, contemplates the giving of the extracts of many glands."

Here, then, was my job: To work out these interrelations from a clinical and therapeutic standpoint; and to facilitate

the treatment of pluriglandular disorders by suitable pluriglandular therapy. This for years has been the chief aim of the writer and the sole object of this laboratory. And the results which have accrued, as indicated by thousands of letters in our files—represented by an occasional quotation in these pages—are little short of amazing.

Pluriglandular Formulas. In considering how to put this laboratory on a satisfactory and self-supporting basis, I decided in favor of building a business with certain organotherapeutic products in order that the profit derived from their sale might maintain the institution and that, as it grows, opportunities might be afforded to develop the suggestions of colleagues who, like myself, have had more or less intangible ideas which have been difficult or impossible of materialization because of limited finances or facilities. I also felt that the community of interests that would result from this effort would automatically further the ideal which I started out to materialize.

Having made this decision, the most natural way to start seemed to be to prepare a number of pluriglandular formulas which I had been in the habit of prescribing or recommending to my medical friends, and ask these friends to use them if they appeared reasonable. These formulas are given and their therapeutic possibilities are discussed in the following pages, and your favorable consideration of them is solicited.

The next development of the work of this laboratory was the production from time to time of small experimental quantities of various organotherapeutic preparations for colleagues; and already this phase of our work bids fair to accomplish much in the way of broadening organotherapy. As I have said, this was the real underlying reason for deciding to begin operations. These preparations are worked out with or without my own suggestions as required; and some very useful combinations already have been developed. It is a source of great encouragement to me to be able also to submit here a number of them with suggestive clinical indications and other data.

The Character of these Products. Wherever possible the accepted pharmacopeial methods of standardization are followed. For instance, the thyroid "extract" contains the prescribed percentage of organically united iodine as required in the U. S. P. IX. Every effort is made to insure effective desiccations, and I feel that from the standpoint of therapeutic efficacy, at least, the preparations of this

laboratory are not excelled, even in France where the practical application of organotherapy is still far ahead of us.

Aside from the care in production and standardization, there is another very important matter to which I must call attention. We have no secret formulas; no camouflage on the labels or in the literature. We do not even use proprietary or trade names. There are no indications upon the labels and no suggestive enclosures in the packages. Every effort is made to be as honorable and professional as possible; yet despite this no one of the stock pluriglandular formulas from this laboratory is passed by the Council of Pharmacy and Chemistry. A number of them were submitted, but they failed to measure up to the Council's standards, not in so far as ethical standards are concerned, but for the following reasons: "Each of the mixtures contains one ingredient or more, which is neither recognized in the U. S. Pharmacopeia nor admitted to New and Non-official Remedies." This means that a glandular extract that has not reached this stage of acceptation and not been included in these lists is inadmissible. In fact, in the same letter, Professor Puckner, from his presumably large clinical experience, states that "there is no evidence that many of these organs have any value whatever when administered by the mouth or in any other way." This I deny as vehemently as I know how. I cannot gainsay the evidence of my own experience, nor can I ignore the numerous statements made to me personally and in writing. Further, there is plenty of evidence in current medical literature to support any reasonably minded physician in the use of, say, desiccated placenta, pancreas substance or even a spermin-bearing extract from the interstitial cell of Leydig from the testes.

The other reason for judging these formulas as inadmissible is this: "In the light of our knowledge the administration of gland mixtures in the host of conditions enumerated is irrational and on a par with the use of the shotgun mixtures once in vogue." From my own standpoint, as well as that of many others, I am glad to say this position is altogether invalid. First of all, "a host of conditions" indeed follow derangements of the endocrine functions merely because so many factors are dependent upon the proper endocrine balance. Secondly, there is a physiological principle, with which Prof. Puckner is probably not acquainted, and which appears to regulate the capacity of those organs that are dependent upon hormone stimuli, to pick up from the blood the well-

named "chemical messengers" which they need *and in the proportion that they need them.* (See the chapter "A Hypothesis of Hormone Hunger.") We must recall, too, that the blood contains all the hormones we know about and probably many more, as well as the opsonins, the agglutinins, the bacteriolysins, the cells, the platelets, the salts, and so on—a "shotgun mixture" indeed; yet the body manages to make its selections very satisfactorily. Pluriglandular therapy is more rational than monoglandular therapy, as experience has shown a thousand times and will continue to show. The subject is more fully discussed in another section. In the meantime we are trying to be as honorable and frank as we can, and I personally believe that I have the right to pass my own judgment and to do as I please in the matter. Whether others agree with me or not is for them to decide. *If it is a matter of results and the patient's best interests, the pluriglandular idea is indeed a very great advance in organotherapy.* I confess that my patients, my colleagues and the friends of this laboratory are only interested in *results* and they are not worried about the ineligibility or the "shotgun" character of the remedy.

We are making the very best preparations available. The contents are standardized when possible, the dosage is accurate, the combinations are based upon long experience, and time after time the use of these pluriglandular stock formulas has succeeded when presumably indicated single extracts had been used without anything like the good results obtained later.

Publications from This Laboratory. For a number of years I have been thinking about endocrine matters and from time to time I have read a paper or published an article on some subject in which I was particularly interested. In addition to this I have written a number of books, to which it may be well to call attention here.

The Organotherapeutic Review. Quite the most practical literature which is sent out from this laboratory is this small, pocket-size, monthly journal which is intended to review the advances in practical endocrinology and, in particular, to keep the profession in touch with the progress in the laboratory. This journal is eagerly read by many thousands of physicians, who have come to look forward to its visits and many of whom confess that they are in the habit of slipping it into the pocket to be read from cover to cover during an O. B. case or at some convenient time.

The *Review* contains editorial articles by the writer on

practical subjects in this field, a number of brief abstracted or translated articles, and a Correspondence Department in which questions pertaining to clinical endocrinology are answered. This little journal will be sent to any physician each month without charge, on request.

Harrower's Monographs on the Internal Secretions is the title of a quarterly publication. Each issue contains a fairly comprehensive study of one subject gathered from widely scattered sources, arranged in a consecutive manner and carefully bibliographed.

The issues for the first year, 1921, are as follows: 1. Hyperthyroidism: Medical Aspects, 120 pages, price $1.50; 2. Neurasthenia: An Endocrine Syndrome, 92 pages, price $1.25; 3. Epilepsy as an Endocrine Disorder, 80 pages, price $1.25; 4. Endocrinology in Pediatrics, 80 pages, price $1.25.

The first issue for 1922 (No. 5 in the series) is entitled "The Adrenals in Every-day Medicine," and consists of a very comprehensive review of this practical subject with many quotations and translations from foreign sources. (120 pages, price $1.50.) Future issues will take up such subjects as Hypertension; Impotence and Sterility; Defective Growth, Mentality and Nutrition in Children; The Endocrine Aspects of Obesity; and Endocrine Headaches: Their Diagnosis and Treatment.

The annual subscription price in the U. S. is $3.00, and abroad, $3.50. Individual issues may be secured postpaid at the prices indicated.

"Essays on the Internal Secretions." For some years I have conducted a Prize Essay Contest, each year offering $500 in cash as prizes for a series of essays on the internal secretions. This has stimulated quite an interest among some physicians, both here and abroad, and already two volumes of quite interesting matter have appeared entitled "Essays on the Internal Secretions—1920" and "1921", respectively.

These contain practical essays on various endocrine matters from the viewpoints of as many physicians as there are essays. Many of the authors are world-known authorities on this subject.

As heretofore, this contest has begun about the middle of the year and closed in November. The prizes were awarded and the collections of essays have appeared early in the following year—each volume bearing the date of the previous year. The price of each copy is $2.50. Information regarding the rules of the contest will be sent on request

to Glendale, and any or all of the books will be sent to physicians on approval.

"A List of Books on the Internal Secretions." To accommodate a growing number of physicians with literary information this pamphlet of 64 pages is published. It is sent gratis to subscribers for *Harrower's Monographs,* and may be had by others at 50 cents postpaid.

A Library Service. For years we have been collecting clippings and reprints on every phase of endocrinology and, especially, organotherapy. Thousands of index cards and published items are available to visiting physicians. We receive literally hundreds of medical periodicals in seven languages and all are read and clipped for the things of interest to us. Every obtainable book on the subject is in our library, and many times we have been able to render a very helpful service to correspondents.

The object of The Harrower Laboratory is to broaden medicine by developing the practically applicable things in the internal secretions. The chosen motto is, *"At YOUR Service."*

SECTION II

THE BASIS OF ORGANOTHERAPY

In this section, I have attempted to set down the fundamentals upon which present-day organotherapy has been built. These ideas are based upon the opinions of many. Not all may agree with them and, especially, some of the practical deductions; but, nevertheless, they have been tested clinically too many times to be as bad as some would have them. A knowledge of these ideas will give the reader a working understanding of the "why" and "how" of a much misunderstood but extremely valuable branch of therapeutic medicine.

SECTION II. CHAPTER I

AN INTRODUCTION TO PRACTICAL ORGANOTHERAPY

Since the remote days of Hippocrates and Galen, and even of Brown-Séquard, the "sponsor of scientific organotherapy," the administration of preparations of animal organs has been used and discarded and used again. It is indeed a study of perennial interest and at no time has this subject attained so great and increasing a vogue as in these last few years. Without a doubt, the extent of this interest has resulted from the stories of remarkable results—a physician cannot keep a good thing from his colleagues very long—and, not, as some would have it, because of the aggressive manner in which we have developed our work.

There are four principal reasons for this interest:

(1) Many experimental and clinical experiences have developed intelligible reasons for previous empirical practices;

(2) The production and standardization of glandular "extracts" (as they still are erroneously called) has attained a degree of excellence which far exceeds the work of previous years;

(3) The results following the use of organotherapeutic preparations sometimes are astonishing, even though other measures calculated to secure benefit have been tried again and again with little or no advantage.

(4) The development of the relation of the endocrine glands and of glandular synergisms above all other things, has put a new aspect upon the whole subject which has attained practical value through the application of *pluriglandular therapy.*

There is an immense literature on the subject. In my recently published "List of Books on the Internal Secretions" (referred to previously) are listed no less than 400 books devoted to the internal secretions, the ductless glands, their pathology and other intimately allied subjects. Perhaps one-half of these are in the English language. Besides these books there are literally thousands of articles and reports on the therapeutics that this increasing knowledge has made possible. The study of organotherapy or, as it has been called, "hormone therapy," is daily gaining in scope and prestige.

Over two years of study in this field in Europe, with numerous visits to Paris—admitted to be the seat of learning in the science of *"opothérapie"*—Berlin, Brussels, Copenhagen, Amsterdam, London and Edinburgh, caused me to have a much greater respect for the subject which did not seem to be in particularly good repute when I left America in 1912. Many conversations with leading investigators in various phases of the subject, stimulated my interest. The literature was studied and a large file of clippings and reprints accumulated. Soon it appeared that much of this information was worth collating and I therefore prepared the manuscript for a book that would introduce interested readers to an extremely broad and fascinating subject which is passing from the stage of academic discussion to that of great clinical value in the routine, every-day practice of medicine.

"No subject will prove more enthralling to the interested reader than the possibilities of hormone therapy, not only in the obvious disorders of the endocrine glands, but in many other diseases evidently amenable to treatment with their products. Nor will the interest wane when plausible theories have become tangible results; for the possibilities of this method are almost limitless; nor is its chemical basis dependent on the unsupported experiences of a few enthusiastic investigators."

Strangely enough, until the year 1914, there was no book in English which thoroughly covered the practical side of this subject and as mentioned in the Introduction, it was my privilege to publish, just before the European war, a book called "Practical Hormone Therapy."* In this book an attempt was made to collate in a more or less comprehensive fashion a majority of the most important facts relating to the many branches of the therapeutics made possible by the advance in our knowledge of the internal secretions and the organs producing them. This information covers such a wide field that the data was divided into 8 sections and 36 chapters. To facilitate the study of this subject, I added a glossary of terms, many of which are now included in the medical dictionaries, an organotherapeutic dose-table and a series of bibliographies directing attention to no less than 793 references, the largest proportion of which directly concern the practical side of organotherapy.

The physician who is sufficiently interested to look up some of the bibliographic references to these various subjects, soon will be convinced of the reasonableness of many of the facts and suggestions which have been gathered there, and a much more complete series of references will be opened up to the student, for the bibliographies of the 800 articles indexed in "Practical Hormone Therapy" direct one to at least 4,000 additional communications! So much for the larger book which, I am glad to say, has been extremely well received and reviewed.

There is no doubt that many a difficult case will prove to be amenable to organotherapy, even after several other things have failed. I frequently find myself recalling experiences in my practice of years ago, that I am confident could have been simplified with practically no trouble—had I known what I now know about organotherapy. Twelve years ago we did not have corpus luteum or pituitary extract to help us as wonderfully as they sometimes do now. It is hoped that the facts collated here may prove to be frequently serviceable to those into whose hands this book may come, and it will be a pleasure to hear from interested readers with criticisms, comments, experiences or requests for coöperation.

The section which follows comprises in truth the merest outlines. No attempt is made to explain the "why" and

* This book is at present out of print though some day it may be rewritten.

the "how." The essential physiologic basis or explanation is missing, as space is not available either for this information or for the numerous clinical experiences and reports which might supplement it, many of which may be found in my other books, or scattered throughout the literature of a dozen countries.

Here is offered the "real meat"—the boiled-down essentials of a subject which, according to Leonard Williams, "already unfolds before the astonished view of the seeing eye, a land of promise besides which the discoveries of Lister and Pasteur are destined to pale into honorable insignificance."

SECTION II. CHAPTER 2

THE ESSENTIAL FUNDAMENTALS

The literature on organotherapy, especially that which has been published during the last ten years, is both vast and comprehensive; and marshals unnumbered facts which have placed this most ancient and altogether empiric form of therapeutics upon a scientific and up-to-date basis. The ductless glands have been studied with enthusiasm and thoroughness, and their importance is being more generally recognized because both the physiologists and the pathologists have definitely shown us a part, at least, of their functions and connected their researches with many heretofore unsolved medical puzzles.

General Considerations. The status of the hormones, or the active principles obtained from certain glands of internal secretion secured from animals, and their use as remedial agents, has arrived at a place which reaches well beyond the laboratory of the physiologist. These active principles are undoubtedly specific substances, and some of them already have been isolated while others are obviously present although they have not yet been chemically separated. These substances have been given the convenient generic name *"hormone"* from the Greek, "I arouse," or "set in motion," and are now known to constitute a series of important chemical messengers by means of which the functions of the body are correlated.

Each hormone—sometimes an organ has the faculty of producing two or more hormones—has the inherent capacity

of exciting to definite activity those cells for which it manifests a special affinity (in this connection note the chapter entitled, "A Hypothesis of Hormone Hunger"), and we are just beginning to appreciate the considerable importance which attaches to the normal production of these different hormones, as well as to the maintenance of the balance which is brought about by the action and interaction of these variously acting bodies.

While organotherapy is undoubtedly the oldest form of therapeutics, it has become the newest, for the good reason that the discovery of the hormones and their influence upon physiology has enabled the students of the past ten or fifteen years to give a reason for many clinical phenomena and thus establish the empirical procedure of Hippocrates, Galen and others of ancient and more modern times, upon a scientific and unquestioned basis.

Pharmacy has contributed its share to the growth of this phase of therapeutics, and much work has been done, especially in France and America, to produce therapeutically active as well as convenient preparations with which to apply in a practical way, the fundamental principles which have been laid bare.

Four Principles. These fundamental principles have been grouped under four chief heads under which the various organotherapeutic procedures may be classified conveniently. These forms of organotherapy are as follows:

1. *Substitutive.*
2. *Homostimulative.*
3. *Empirical.*
4. *Specific.*

A very brief consideration of each of these four forms of organotherapy will explain, in part, its scientific basis, and enable the interested reader to classify the animal extracts from a therapeutic standpoint, though in a somewhat different manner from the classification used in the subsequent pages in which the various organotherapeutic products are arbitrarily divided into three classes according to their present popularity and therapeutic availability.

Substitutive Organotherapy. Properly prepared extracts of various glands supply a deficient physiological secretion of organs that correspond to those from which the extracts are made. The disorder may be due to absence, atrophy or functional inactivity of these organs, i. e., the production of their normal active principles has been reduced or stopped. A typical illustration of this category is the use of thyroid extract to replace the secretion which is missing, as in myxedema.

Homostimulative Organotherapy. The active principles of the internal secretory organs have a definite stimulative and restorative action upon the glands corresponding to those from which the extracts are made. It has been remarked by some French writers that organic extracts exert a regulative action upon the organs from which they are derived, not only favoring the restoration of their functions, but also of their normal anatomic structure. Hallion is prominent among these and his "law" briefly states this principle as follows:

"Extracts of an organ exert on the same organ an exciting influence which lasts for a longer or shorter time. When the organ is insufficient, it is conceivable that this influence augments its action, and, when it is injured, that it favors its restoration."

This principle is the basis of a large share of the value of organotherapy, and is represented quite typically by the use of bile in hepato-biliary insufficiency, or ovarian preparations in functional ovarian disorders.

Empirical Organotherapy. Certain animal extracts seem to influence certain clinical manifestations and as a result have come to be used without a definite and acceptable scientific basis. Examples of this form of organotherapy are the pituitary treatment of functional ovarian disorders, or the parathyroid treatment of paralysis agitans.

Incidentally, as our appreciation of the intricacies of the endocrine relations grows, the empirical use of organotherapy will disappear and in its place we will put some other form. Already this may be true of the two examples just mentioned.

Specific Organotherapy. Finally, it has been found that extracts of certain organs exert a definite physiological influence, not by virtue of a homostimulative action, but by causing certain physiologic activity, or by counteracting some particular morbid symptoms not due to any change in the internal secretory action of the glands of the patient. The most decided and remarkable type of this class of organotherapeutic remedies is the extract of the posterior lobe of the pituitary body represented by *Liquor Hypophysis, U. S. P. IX* (Harrower), and its effect upon the uterine muscle, especially during labor.

Until quite recently it was the exception rather than the rule to find physicians having every-day recourse to the various hormone-bearing products, and while the administration of thyroid, adrenal, ovarian and pituitary extracts

is quite general, it should be remembered that their therapeutic value was demonstrated before we knew that their activity was really in their contained hormones—before our present more extended knowledge of this subject had been attained.

It seems quite reasonable to presume that if, say, desiccated sheep's thyroids suffice to supply the lack brought about by thyroid insufficiency in the human, and that other glandular extracts serve to produce equally valuable therapeutic results, hormones produced in the glands of animals deserve to be more generally used as remedies; and the administration of the various specific glandular activators should become both a common and important factor in the practice of medicine.

Favoring Cellular Rest. It has been previously remarked that the administration of glandular extracts frequently serves as an actual stimulus to the work of the organ corresponding to that from which the extract was made. This may be accomplished by temporarily relieving certain overworked cell collections from the necessity of manufacturing their normal product, and thus allowing them rest, to recuperate and regain their lost or diminished function. Again, this action may be brought by the specific influence which these hormones are presumed to exert upon the precursors of hormones in corresponding organs—it has been quite thoroughly established by Hallion, of Paris, that the administration of secretin in addition to bringing about the activation of various digestive zymogens and their liberation from the pancreas, liver and intestine, definitely favors the production of an increased quantity of the precursor of secretin (prosecretin) in the duodenum itself, as well as causing an increase in the blood supply to that particular part. *In other words, the ingested hormones also may be "made over" or used again,* just as bile is reused by the liver after its alimentary service has been accomplished. Another equally important field of usefulness for the hormones is to supply immediately to the system substances for which it is craving as, for example, the use of the dynamogenic principles which regulate the so-called "adrenal system" and which are deficient in asthenic, run-down states, or ovarian extract in the disorders which follow the artificial menopause, etc.

If it is possible to procure from animals the substances which serve to activate certain of their functions, and by introducing them into the human body, to accomplish for

the patient what these were intended to have done for the animal, is there not a most reasonable philosophy and foundation for the more general application of hormone therapy?

As Leonard Williams, of London, remarked in the preface to his book, "Minor Maladies": "I believe that the serious study of what are called 'minor maladies' will lead to the prevention and forestalling of many serious diseases. Still more earnestly do I believe that the study of the whole field of the internal secretions will enable us to detect and correct morbid tendencies with a degree of success which has been denied to the older methods. The microbe—the seed—has ruled the immediate past; the future is with the soil, the endocrine glands."

It must be remembered that the dosage of products that are active as a result of their hormone content has quite a different basis from that of drugs: There is no definite dosage, save "dose enough." Joseph Pratt, of Boston, has said: "As all internal secretions are stimulatory substances and do not furnish nutritive material to the cells, they are able to exert their specific action when present in very small quantities."

To one who uses the hormone-bearing extracts for any length of time, and who thus has an opportunity to appreciate their specificity and value, the subject assumes a most important aspect, since it makes possible results otherwise unattainable. In the words of Leonard Williams, this is "a subject of inquiry as fascinating as any in the whole range of medicine, and as fruitful in promise as any in the whole range of therapeutics."

SECTION II. CHAPTER 3

FAILURES WITH ORGANOTHERAPY

As with every phase of the treatment of disease we expect to encounter a certain proportion of failures with the administration of organotherapeutic preparations. It could hardly be otherwise, for we have not found the long-sought *"Elixir Vitae"* which Ponce de Leon and others have vainly looked for.

If we are wise, our failures will become our greatest assets, for through them we may learn more than in any

other way. A graduate from the "University of Hard Knocks" always is a better posted and more dependable man than the one who has secured most of his information easily by avoiding the failures of others, though, naturally, our course in this "university" can be shortened materially by being awake to what others are doing.

During my experience I have often heard statements something like this: "I tried that treatment faithfully for several weeks, and it seemed to do no more good than other things we used before. I'm afraid I haven't much use for . . . ."—corpus luteum, mammary extract, or even thyroid gland have been mentioned. At times organotherapy as a whole thus has been criticized, despite the apparent limitations of the speaker's clinical testing.

This profitably may be used as the text for a short "sermon" which may develop some helpful suggestions for those who are expecting great things from organotherapy, and to whom it may be a somewhat new procedure.

The Usual Run of Cases. First of all we must admit that usually organotherapy has been tried in difficult cases of long standing where other measures have been tried, perhaps repeatedly and by many physicians, and have failed. Here, naturally, the results will be less satisfactory just as any treatment is likely to be less effective the further advanced and more complex is the disease. It is true that organotherapy deserves consideration in just this class of cases, for it has been remarked many times that when other things have failed, organotherapy has enabled us to get wonderful results, and, perhaps, we may have acquired an undue enthusiasm, and expect too much of this method. None the less we must not deprecate organotherapy for this reason merely because we cannot use it to accomplish the impossible.

There is another very important factor that sometimes seems purposely to be ignored, especially by those who don't want to be convinced! We have seen that the real basis for the benefits to be expected from organotherapy lies in the principle of homostimulation. This means that we must have active preparations and responsive organisms. It is possible to have an inactive remedy, I will admit, though in these days such products far excel those of years ago; but how about the reactivity of the patient and the response of those cell-aggregates that it is desired to arouse or set into renewed motion? Especially in chronic disease where the conditions are results of constant and long-continued

irritation, malnutrition or toxemia, the reëducation of the worn-out endocrine glands is no small task. And too, the degree to which the endocrine glands are affected in one case as compared with another seemingly quite similar, varies very much indeed. Again, there is a very decided though intangible individual element, for one person responds to hormone stimuli rapidly and thoroughly, while another does not. One child "catches everything going," while another "has never been sick in her life." It is merely a matter of the physiological substratum—and this indeed is an indefinite quantity.

Nevertheless we will continue to use organotherapy expecting a certain percentage of delayed results and even some entire failures, and are more than satisfied with the numerous excellent responses to the natural hormone stimuli that the administration of glandular extracts makes possible.

Need for Prolonged Treatment. Another cause of failure is due to stopping before one should. In our "text" above, "several weeks" is the time stated as being the limit of the doctor's patience. Now organotherapy is useful largely because it is a means of educating certain organs to perform their service to the body as a whole. Education is not a matter of days or even weeks. It takes many years to educate the mind. The gastro-enterologist knows that it takes months to educate the liver, gastric cells or other organs to perform the task which through various circumstances has been given up or done unsatisfactorily. When we give morphia we expect practically immediate results. It works quickly, not by "education" but by paralyzing certain functions. Strychnia also works quickly, not by "education" but by abnormal stimulation, and how long do such effects last?

As a matter of fact, the subtle influence of hormone therapy is indeed a reëducation of certain organs, and this always takes time and, as we have seen before, depends a great deal upon the responsiveness of the cells. To be successful organotherapy should be added to other treatment, drug, hygienic or dietetic, and should be continued always for a generous time; and further, it should be "tapered off" to see how well the endocrine glands can get along without these additional stimuli.

The Pluriglandular Idea. Still another potent cause of failure is the not unusual tendency to ignore the intimacy of the ductless glands and their most important interrela-

tions. The subject of reënforcing this extract or that is given comprehensive consideration elsewhere in this book; and I merely mention as one of the causes of failure, a habit of overlooking associated derangement of other glands which are dependent upon or at least associated with, the particular ductless gland which may have been discovered to be at fault and which is being treated with organotherapy. In other words, *combining synergist gland extracts is likely to make for better results;* and here, let me say with emphasis, is the "open sesame" to the successful application of organotherapy in a generous percentage of all cases in which this measure is indicated. I have repeatedly asserted, and it has not yet been denied, that *it is not possible for a single endocrine organ to be affected, slightly or seriously, without reflex (hormonic) effects upon others of the allied organs.*

This aspect of the matter is so important that it is given more consideration in several chapters of this book. The *"pluriglandular idea"* is as great an advance as has been made in organotherapy despite a few criticisms from those without clinical experience who, having at one time definitely committed themselves as opposed to such "shotgun methods," must now keep up the fiction, or be turncoats!

Useful in Functional Disorders. There has been a good deal of comment, especially in some manufacturers' literature, about the organotherapeutic treatment of certain organic diseases, especially of the central nervous system. These statements have led some to expect "cures" in such diseases as locomotor ataxia, multiple sclerosis, paralysis and other diseases generally conceded to be "incurable." I do not deny that increased endocrine function is likely to be helpful in an organism afflicted with such diseases as those mentioned just as in any others, but it does not replace the destroyed nerve cells, and can not. Organotherapy may be indeed helpful in such hopeless cases, but it is far from curative and it should be obvious that if this method really cured locomotor ataxia, the manufacturers and their fortunate medical customers would never lack either opportunities to serve or the financial rewards which would naturally come with such a service. Organic disease is not amenable to organotherapy in the degree that we expect functional disease to respond to it—it simply cannot be so.

The One Great Cause of Failure. Finally, quite the most important of all the causes of failure with organotherapy (and, for that matter, any other method of treatment) is

an incomplete diagnosis. Too often we learn what is the matter with our patient, but not *all* that is wrong. I have repeatedly stated that the medical profession commits more sins of omission than of commission. We overlook things. Why, the minor form of hypothyroidism is more than commonly ignored entirely! The consideration of the endocrine side of the ordinary troubles which are met every day in general practice has been passed by until very recently. Disorders of the ductless glands had to be "real diseases" before we recognized them, and hidden functional aberrations were never sought for. Now all is being changed and as our eyes are being opened to the importance of *functional pathology* not only are we recognizing the early influence of endocrine dysfunction, but we are learning to consider our patient as a whole rather than as an individual with some obvious disease.

Here, then, lies the greatest source of failure in medicine —we have been treating diseases rather than patients! So long as we consider a case of, say, hypothyroidism as being suited for organotherapy and ignore the demineralization, the acidosis or hypoalkalinity or the original active cause of the disturbance—some hidden focal infection, a dilated and overloaded colon, a dietetic habit (such as coffee-drinking) which has overburdened the detoxicating department of the body or other common underlying causes of disease—we are not going to get the optimal results from our organotherapy.

The reverse is equally true—even if we are most thorough in our diagnosis, and our clinical and laboratory findings are about perfect, we can reduce the efficacy of our treatment quite considerably by omitting to consider the effect that the various derangements may have had upon the endocrine functions and with this information in mind, make a concerted effort to encourage these overworked glands and favor the reëstablishment of their normal functional service to the body in conjunction with the other obvious things we need to do.

There are other causes of failure with organotherapy which will occur to the thinking physician and which need not be mentioned here. For instance, if one is convinced that a certain procedure is destined to fail, likely as not it will! If the patient is sure your measures are not going to help, the psychic condition may indeed overbalance a large part of the possible benefit. So with organotherapy. We must realize that it is but a factor in our work and that we

cannot and must not expect the administration of a few tablets or capsules to reëducate, rejuvenate and remake our patients.

SECTION II. CHAPTER 4

"THE PLURIGLANDULAR THEORY"

A fundamental principle which, to my way of thinking, has broadened organotherapy in a very decided manner is embodied in the following statement: "Pluriglandular disorder is much more frequent than disorders involving a single gland of internal secretion; hence the reënforcement of an indicated organotherapeutic extract with one or more synergists many times radically alters the results for the better. In fact, it may make the difference between success and failure."

It is not difficult to understand that a general influence for harm—toxic, nutritional or emotional—hardly can be expected to limit its effects to a single small part of the organism. A severe toxemia such as we find in pneumonia, typhoid fever, intestinal stasis or poisoning with alcohol, morphin or other drugs, deranges the function of the body as a whole although in one instance a certain part of it, say the liver, may be more obviously disordered than another. This applies equally to the endocrine glands, and the writer frequently has said with emphasis that *"there never was a uniglandular endocrine disorder!"* This may seem to be a rather inclusive statement; but it would be difficult to convince me of the reverse, for once one has learned the principles underlying hormone action and the extreme intimacy of the endocrine glands as well as their close dependence the one upon the other, it is not easy to conceive of any obvious or hidden disease process affecting only one or two of these remarkable little organs to the exclusion of the others. They may be remotely situated from one another, but they are very closely bound together by their hormone duties.

Indeed, students of the subject have found the strands of thought closely intertwined and practically no writer on the subject, when giving consideration to one special gland, has succeeded in omitting to refer to some coincidental influence or relation between that gland and certain others.

Clinical Endocrine Relations. The subject is so important and the clinical and therapeutic deductions are so valuable that it may be well to give some more attention to this "theory." Take as an example a fairly common ductless glandular disorder—hypothyroidism. It is seen in all gradations, and its own direct manifestations are always intertwined with those of other origin. No case of myxedema or cretinism, or even of the less marked but more important minor forms of thyroid insufficiency, shows the manifestations of thyroid dysfunction alone. Metabolism as a whole is reduced—and the thyroid is not the only endocrine gland concerned in the regulation of metabolism. Gonad function is disturbed, and in cretins it practically never develops at all.

The thyroid gland exerts a very marked coöperating influence upon the function of the gonads, and perhaps more so in the case of the ovaries than the testes. Thyroid disorder is so very commonly associated with menstrual functions that the gynecologist should never consider a case of menstrual derangement without also considering the thyroid function with that of the ovaries.

I might say in passing, that the idea of considering the intimacy of the thyroid and ovaries came to me as I was studying in Paris a number of years ago when I accidentally ran across some information which seemed interesting to me at the time, but has grown very materially in importance since then. Paul Dalché, one of the physicians at the famous old Hôtel Dieu, routinely ordered a combination of thyroid with ovarian substance in all ovarian cases that came to his gynecological dispensary service there—the only exception to this routine being in cases obviously suffering from thyroid irritability. The reason for this treatment was very brief: "The thyroid is routinely involved in these ovarian cases."

The pituitary gland, likewise, in addition to its large influence upon the metabolism, exerts a stimulating effect upon the sex glands, and there is plenty of evidence to show that the pituitary coöperates with the thyroid in initiating and maintaining normal sex gland activity. A casual clinical experience, which the student of endocrinology often meets, concerns the condition known as pituitary headache. In many women, especially where there is an ovarian dysfunction, during the period just prior to menstruation, there is a very serious headache of the splitting, rending variety. This headache usually ends at the establishment of menstru-

ation and is not noticed until the corresponding period of the next month. It has been found that these cases benefit very materially by pituitary feeding, and a logical deduction in regard to the *raison d'être* of this is that the pituitary gland, discovering that the ovaries are not working as normally as they should, becomes functionally hyperactive and consequently, engorged, and this increase in its size (it will be remembered that the pituitary gland lies in a very limited bony space called the sella turcica) causes an intracranial tension, with a consequent pressure headache. As soon as this pituitary engorgement is made physiologically unnecessary—either by the regulation of the ovarian trouble or the replacement of a part of the missing pituitary principle by organotherapy—we relieve the cause of the headache and it disappears forthwith.

The adrenal glands, transcendently important in those reactions of the body to poisoning and emotional circumstances, influence practically all of the ductless glands through their motor effects upon circulation. When the adrenals are stimulated, muscular and circulatory tone is increased, the nutritional exchanges are enhanced, and in general there is an acceleration of metabolism and all cellular function. Hyperadrenia means a general excitation of the sympathetic system and endocrine function as a whole. On the other hand, unfortunately the adrenals are very easily overstimulated and played out, with the result that there is a circulatory stasis, muscular atonicity, and general asthenia which naturally extends to the other ductless glands, bringing about not merely a hypoadrenia, but a hypocrinism, or a generalized insufficiency of the entire ductless glandular system.

The sympathetic system, which we have every reason to believe is controlled by the hormones produced in the chromaffin tissue of the adrenal glands, is very decidedly affected in hypothyroidism, and in the well marked cases the blood-pressure is low, circulation is very much below par, and the usual sympathetic reactions are dulled or even lost.

Again, the so-called "compensatory hypertrophy" of some glands during functional or organic insufficiency of some other intimately associated gland of internal secretion adds to the impression that these organs must be considered together rather than separately. The cycle of the development and atrophy of the mammary glands in relation to the variations of the ovarian function is one instance. The not infrequent enlargement of the thyroid (and more rarely

the pituitary) during the period of normal ovarian inactivity—during gestation and at the beginning of the menopause; possibly the interstitial glandular hypertrophy of the prostate when the testes are in process of normal atrophy; and other physiological functional dependencies which we do not need to mention, all tend to the conviction that we must no longer consider endocrine disease, functional or organic, as involving the gland or glands alone which most obviously are affected.

Synergistic Organotherapy. This being the case we should be able to make good use of the principle in our work, both diagnostic and organotherapeutic; and the added information that we acquire by viewing various symptoms-complex from "the pluriglandular viewpoint" is just as encouraging as the better results that we get from pluriglandular, as compared with uniglandular, endocrine preparations.

Clinical experience has established this beyond all doubt—literally thousands of cases of obvious dyscrinism, having been treated with single endocrine products without satisfactory results, have, on changing to an indicated pluriglandular remedy, shown results as different as they are remarkable.

In brief, then, the facts warrant the combination of synergistic gland extracts no matter whether we can see clear clinical evidence of disorder of these synergistic glands. It must be remembered that symptoms do not necessarily manifest themselves for quite some time after the beginnings of actual dysfunction in the cells. The ovarian side of goitre, or the thyroid side of dysovarism, does not always accompany the first evidences of disturbed secretion in the gland originally affected.

Nor must we limit our new viewpoint to pairs of organs like the thyroid and the gonads just referred to. In hyperthyroidism, for example, not only may we find deranged ovarian function, but I am confident that not a few of the symptoms of sympathetic irritability are not so much due to the excess of thyroid stuff itself as to the undue stimulation by it of the adrenal glands. Really then what we call hyperthyroidism often is hyperadrenia (!) or hypercrinism —a generally increased endocrine activity due to a condition which has increased thyroid secretion beyond all reasonable bounds and consequently simultaneously has stimulated the pituitary, adrenals, gonads and other endocrine glands. If this is the case, medication to be success-

ful should take the whole endocrine system into consideration and not the offending thyroid alone. The same applies even more to conditions of hypocrinism which result from pluriglandular insufficiency.

Antagonistic Organotherapy. Another interesting aspect to this study is the antagonism which may be exerted between glands of internal secretion. The islands of Langerhans in the pancreas are known to have a large part in the regulation of the metabolism of carbohydrates and, incidentally, to exert an opposing influence upon the adrenals. This is so well-defined in the experimental work that has been done along these lines that a new classification of internal secretory principles has been demanded merely because the word "hormone" means "I arouse" or "set in motion," and the chief function of the hormone from the islands of Langerhans is to prevent too much "motion" on the part of the adrenal glands. The French call this Langerhansian principle an "anti-hormone," and von Noorden has called it "the brake to the sugar mechanism" merely because it prevents an overoxidation of sugars and restrains adrenal activity.

This particular principle is used in organotherapy to control overirritability of the adrenal glands, to lessen the condition known as "sympatheticotonus", to reduce the imbalance in hyperthyroidism, and also in diabetes mellitus.

Another and equally remarkable hormone antagonism concerns the influence that the mammary glands exert upon ovarian function. The mammae undoubtedly have a dual function, and in addition to their galactogenous influence they undoubtedly oppose ovarian activity. The physiology of mammary growth and function tends to supplement this impression, but our best information comes from the use of mammary therapy in conditions of ovarian irritability, and particularly menorrhagia. It has been found repeatedly that mammary therapy is a well-conceived anti-ovarian remedy, and for this reason the internal secretory principle believed to be present in the mammary tissue, has been called, like the pancreas principle, an anti-hormone.

Nothing has been said about the parathyroids, pineal, the carotid glands and certain other secretory organs like the liver, the duodenum, etc., which have an internal as well as an external secretion. Suffice it to say that all form a part of a large, well-ordered and complex mechanism which deserves consideration as a whole whenever any one part of it is deranged.

Combinations Superior to Single Extracts. This all explains why combinations of various endocrine preparations so often excel single extracts. In previous communications, and in both of my books referred to elsewhere, I have strongly urged the combination of suited products of this kind. The profession is thoroughly converted to moderate polypharmacy, and we combine our A. B. & S., or our I. Q. & S., our mercury and potassium iodide, or many other well-known pharmaceutical products. Rarely is a prescription written for a single remedy, for we are absolutely convinced that synergism is possible in pharmacology just as it is in physiology. Should there, then, be any real basis for criticism of pluriglandular therapy by those who routinely apply the same principles in polypharmacy, especially when we recall that the blood itself contains in solution a host of differing chemical substances, some synergistic and some antagonistic?

As a matter of fact, such portions of a pluriglandular mixture given *per os* as are absorbed in the blood, merely amplify the sum total of hormones circulating in the blood according to the principle of homostimulation already outlined, and arouse to increased functional action those organs whose work it is to produce hormones similar to those which have been administered. Thus hypocrinism is reduced and the aggregate of hormone stimuli is increased.

Certain aspects of the correlation of the glands will be referred to in later chapters when particular syndromes are being given consideration from the clinical standpoint. It seemed advisable to include these brief hints here merely because so many physicians are at sea when they come to consider the actual relationship that these glands bear to one another.

SECTION II. CHAPTER 5

A HYPOTHESIS OF "HORMONE HUNGER"

The following remarks originally constituted a communication which was published in the New York *Medical Record* (August 16, 1919). I am pleased to state that it aroused considerable favorable comment and, by many physicians, has been accepted as a reasonable explanation of what really happens in the cells which depend upon hormone stimuli.

Certain fundamentals in medicine as in other sciences necessarily must be based upon hypotheses, for it is not accorded to man to know all about the Creator's work. We are confident that scarlet fever, measles and even "flu" are of bacterial origin; but we have yet to isolate and identify the offending organisms, as we have done, for instance, with the typhoid bacillus. Again the "accepted explanation" of the processes of immunity is the so-called "side chain theory" propounded by Ehrlich; and today this hypothesis is as far as we can go in giving a reason for the "immunizing response" of the body and the "how" of its resistance to bacterial invasion.

The clinician has to presume many times. Facts are not always so easy to secure. On the other hand, the physiologist hesitates to presume—he must be scientific and empiricism has no place with him. Despite this it happens that neither clinician nor physiologist really understands how the hormones of the glands of internal secretion are made and used. We have satisfactorily proved their existence and that many of them are definite chemical entities, some of which already have been isolated in crystalline form. We are certain that they are secreted into the blood or body fluids and thus carried to distant organs or cells to "correlate the activities of the organ of origin with the remote but associated organ that it influences."

How these hormones are carried, whether they are produced in the same form that they are used* and exactly how they reach the cells which they are destined to "arouse, or set in motion," is not known. A hypothesis is in order.

For a number of years I have been studying this subject and not a few clinical experiences with various forms of organotherapy in certain endocrine disturbances have convinced me that there are varying degrees of receptiveness to hormone stimuli on the part of various individuals. In other words, where in one instance a very rapid and remarkable result may be secured, in another seemingly similar case the reactivity of the patient differs and the results are not so good or so rapid. This has caused me to ponder on the subject and I have evolved what I have chosen to call "a hypothesis of hormone hunger."

* In 1913 I had the opportunity of doing some interesting work with Hustin in the Institut Parc Leopold, Brussels. He showed that secretin activated the secretory cells of a pancreas separated from the body—in a paraffin bath; but the most active secretin solution *had to be mixed with blood* before it would do the work.

Selecting the Hormones from the Blood. Each organ of the body that is dependent upon hormone influences must have some subtle capacity to pick up the hormones from the blood as they float by. This cannot but be true, else how could the passing "chemical messengers" bring about the influence upon the organ or cell that they are supposed to affect? Not only must there be a definite capacity to pick up these hormones as they are brought to the cell by the blood, but there must be a selective capacity, for the blood contains all the hormones that we know of as well as probably a good many more that we do not know at present. I do not feel that the imagination has to be stretched very much to presume that there is a remarkable "cellular judgment" or selective capacity to pick out the hormones that are needed—*and in the amount that they are needed.*

It is with this particular selective power of mind that I have developed this hypothesis of hormone hunger. I contend that under varying circumstances these cells must be more active in their picking up of the passing hormones than at other times. In other words, at times a condition of hormone hunger actually must be present. Let me explain: Take as an example the thyro-ovarian interrelationship—this is, perhaps, the most thoroughly established and most easily understood. It is well known that there is a principle produced in the thyroid gland which exerts a very marked influence upon ovarian function. (It will be recalled that in myxedema there are definite functional ovarian disorders, that girls with goitre very often have serious menstrual difficulties and, finally, that the cretin, who has no thyroid gland, does not develop sexually.) Surely it is fair to believe that there is a principle made in the thyroid which stimulates ovarian function, and that this must necessarily reach the ovaries through the blood, and, of course, that the ovaries must have some means of getting hold of this hormone. If, then, this thyroid hormone passing through the ovaries in its blood supply happens to be deficient, after as much of it as can be found is taken up by the cells of the ovary, and the demand is greater than the supply, there will remain a need for that which is not present, i. e., the ovarian cells will be "hungry" for more of the thyroid stimulus. Further this "hunger" will vary, depending upon the degree to which the thyroid is functioning and the hormone needs of the ovary.

A Case in Point. In a case with well defined hypothyroidism it is reasonable to suppose that the ovarian cells are

getting along as best they can with little or none of their usual stimuli (and right here enters the fascinating study of the effects of hormone hunger upon other endocrine glands—how the pituitary, for instance, may function faster to make up for deficiencies in its associates, etc.) If we attempt to modify the clinical disturbances which result from this hormone insufficiency by means of organotherapy, the application of this hypothesis enables us to appreciate that the "hormone hunger" of these ovarian cells increases their presumed "urge" to pick out from the circulation such additional hormones as we may be able to give by mouth (and incidentally to benefit from the enhanced hormone production which follows organotherapy, upon the principle of "homostimulation" as outlined in Hallion's law*) and to understand that this selective capacity will be the greater in proportion to the cellular need for the accustomed hormones which happen to be deficient.

To put this in another way: If we give thyroid extract as a therapeutic measure in dysovarism, the ovaries are unusually interested in securing the thyroid hormone which may get into the blood, and they will select it with greater avidity, depending upon the degree of "hormone hunger" that may be present; and as soon as the necessities of these glands have been satisfied the unusual facility with which the hormones are picked out from the blood stream will cease, and we presume that superfluous amounts of any or all of the hormones will remain in the blood either until they are used later on by any organs that may be able to avail themselves of their stimuli, or are finally oxidized.

There is another phase of this matter which appears to me to be of importance, and which I think is more satisfactorily explained by this hypothesis than in any other way. We are convinced that the intimate interrelationships of the glands of internal secretion practically eliminate the possibility of endocrine disturbances involving a single endocrine gland. That is to say, when there is a disturbance of one internal secretory organ, immediately there develops an associated functional derangement of the hormone balance,

* The "law" propounded by Hallion (*Presse Medicale*, 1912, xx, 433), explains the principle named "homostimulation." It is as follows: "Extracts of an organ exert on the same organ an exciting influence which lasts for a longer or shorter time. When the organ is insufficient, it is conceivable that this influence augments its action, and, when it is injured, that it favors its restoration." (Translation made in my book "Practical Hormone Therapy," p. 24.)

involving one or more of the glands most intimately dependent upon the originally affected gland. Hence pluriglandular disturbances are the rule, and therefore pluriglandular therapy must take the place of the old-fashioned administration of the most obviously needed glandular extract. As yet this position is not generally accepted, and some members of the profession still assert that this is "shot-gun therapeutics." Others, whose clinical experience and viewpoint are broader, now insist that in the combining of various related glandular products we are finding much greater clinical satisfaction—and the "crucible of the clinic," as George W. Crile calls it, is the only real test of any new or modified therapeutic measure. In passing, take as an instance the cretin, who it is well known is in dire need of the physiological stimulation resulting from the thyroid hormones. Many times a cretin develops remarkably on thyroid alone, and then reaches a seeming barrier beyond which no progress is made. If, then, the associated glands, especially the anterior pituitary is given *with the thyroid,* the progress is reëstablished and sometimes far excels that previously made. This also applies with equal force in many other pluriglandular dystrophies, the most common of which is the thyro-ovarian dysfunction already mentioned.

An Explanation of Pluriglandular Therapy. This brings me to my final point: This hypothesis of hormone hunger explains the "how" of pluriglandular therapy. Many times I have wished that it were possible to determine the degree of glandular insufficiency in a given individual, just as we can estimate the urinary solids and differentiate the percentage of urea, chlorides, phosphates, etc., in figures, or as we do in the differential blood count. It would be ideal to be able to establish that, for example, a given case is 50% low on thyroid, 75% low on ovarian, and 20% low on pituitary hormone functioning. Obviously this would facilitate a fairly definite therapeutic recommendation; but we cannot do this, although my Thyroid Function Test (see *Medical Record,* August 3, 1918) is quite a step in this direction in the study of one of these dyscrinisms.

How, then, can we treat these cases scientifically? We cannot; but by depending upon the hypothetical principle of "hormone hunger" just enunciated we can offer a pluriglandular mixture *and allow the body to do its own selecting.* We can trust the organism to pick out from the menu we offer it those hormones that it needs most and, too, in the degree that it needs them. Then, based upon the pre-

viously mentioned condition which might be called "hormone satiety," the limited excess of unused hormones floats on until used up or destroyed. This explains to me the reason for the clinical experience many of us may have had with the same pluriglandular therapy in several somewhat dissimilar cases: In one case a thyroid influence predominates, in another a pituitary and the third an ovarian, all because in these three instances the hormone hunger made it possible to grab the various respective hormones with a greater avidity and rapidity.

Whether this hypothesis is as well founded as the Ehrlich "side chain theory" of immunity, is not for me to say. It explains many things that I have seen repeatedly in clinical organotherapy and I believe it is based on sound reasoning and worthy of consideration. At all events this remarkable selective capacity of the hormone-influenced organs or cells is something that cannot be gainsaid; and the clinical results are certain enough whether the hypothesis is well-grounded or not.

Since the original publication of the foregoing chapter in the New York *Medical Record* (August 16, 1919), many references have been made in various periodicals to this hypothesis. The following editorial, which appeared in the *Medical Review of Reviews* (New York, Jan., 1920) is being reprinted despite certain unavoidable repetitions:

"'**A Hypothesis of Hormone Hunger.**' Henry R. Harrower, of Los Angeles, in the New York *Medical Record* for August 16, 1919, sets forward a theory in regard to the manner in which the glands of internal secretion respond to the various hormone stimuli and to a condition called 'hormone hunger,' which may explain some matters pertaining to endocrinology, and especially the administration of gland combinations in pluriglandular dystrophies.

"Harrower presumes that there must be some facility on the part of the various glands which are stimulated by hormones from other internal secretory organs to pick out these various substances from the blood as it passes through them, and suggests that if the supply of the stimulating substances is lessened there will naturally ensue a condition of hormone hunger or insufficiency as a result of the deficient supply of the stimulating substances. Naturally this condition of hormone hunger would be dependent upon (1) the necessities of the gland that is to be stimulated, and (2) the deficiency of the stimulating substance produced elsewhere.

"There seems to be no way of proving this matter definitely, but since one of the greatest factors in therapeutics is dependent upon a theory—the principles of immunity are based exclusively upon a theory suggested a number of years ago by Ehrlich—it may not be out of the way to presume some in this matter also. Attention is called to the relationship between the thyroid gland and the ovary. It is well known that these glands exert a reciprocal action upon one another, each being stimulated by the other, and vice versa. If, then, there is a condition of thyroid insufficiency there will naturally be a deficient activity on the part of the ovaries manifested by such symptoms as amenorrhea, dysmenorrhea and the numerous neuroses connected with menstrual disturbances and the menopause, and at the same time a condition of unusual need by the ovary for the stimuli will obtain. This is what Harrower calls 'hormone hunger,' and he believes that the degree of desire or necessity for these various hormones on the part of the gland that is to be stimulated must vary with the supply of the hormones that can be found in the blood.

"The practical application of this idea concerns the administration of combinations of glands in presumed pluriglandular disturbances. If, for instance, in the conditions mentioned above there is a noticeable deficiency in several of the glands of internal secretion, the thyroid, ovaries and pituitary gland for instance, there may be varying degrees of hormone hunger on the part of the organs involved, and this will influence very definitely the amount of hormones that may be missing or needed by the glands to be stimulated. In such a pluriglandular disturbance, if the thyroid element were greater than the ovarian element, the avidity with which the thyroid part of a pluriglandular formula was used would be dependent upon the degree of hormone hunger on the part of the thyroid gland, and if any other gland was in greater need proportionately its capacity to pick out the hormones from the blood would be sharpened so much the more. In other words, the greater the hormone need, or 'hormone hunger,' the greater the capacity to select from what may be given to it in the way of organotherapy.

"This hypothesis seems to be based upon sound reasoning, and explains quite a number of things in regard to organotherapy, and especially the varying reaction to the same pluriglandular formula in different cases. For instance, in a case of amenorrhea, due to a pituitary dystrophy, the

pituitary element would be accepted more quickly than the other elements in the formula, while if the ovarian element predominated this factor would be both quickly and thoroughly used up. It is then presumed that any product of an endocrine character that may be given in a pluriglandular formula that may not be actually needed immediately would be allowed to pass around in the blood until the necessary hormone hunger was aroused, or until finally oxidized."

Some Criticisms of Harrower's Hypothesis. The chief criticism of this hypothesis seems to be based upon the opinion that excesses of a given hormone are not necessarily allowed to pass by, as I suggest. For instance, in a personal communication, Dr. Solomon Solis Cohen, of Philadelphia, writes: "I have no doubt whatever that various tissues exercise a selective action on substances circulating in the blood, otherwise there would be no physiology or pharmacology to study. Also there is such a thing as saturation of tissue so that it will not take up any more of a certain substance; but whether we can lay down an absolute rule that tissues needing a definite hormone will take up . . . just the amount of that hormone which they need, and no more and no less, is another matter. . . . In exophthalmic goitre, for example, in which an excess of thyroid function is observed, certain tissues at least take up more of thyroid hormone than they need. (I do not, and never have, looked upon Graves' disorder as primarily a thyroid disturbance; the thyroid excess is part of it.)

"According to your theory, the excess of thyroid should be carried out of the body or destroyed without creating any disturbance, but it is not. . . . I am not drawing any conclusions; I am merely pointing out the necessity for realizing the limitations of our knowledge. Every earnest attempt to throw light into the darkness, whether by hypothesis or experiment, should be welcomed."

Dr. Solis Cohen is not the only one to criticize this particular point in my hypothesis. For instance, in *American Medicine* (September, 1921), James C. Wood, of Cleveland, Ohio, discussing the practical application of organotherapy, remarks: "It seems to the writer that the weak point in Harrower's hypothesis, upon which pluriglandular therapy is based, is that, while it may apply to fairly normal individuals, it most emphatically does not apply to those cases where there is hyperfunction of certain of the endocrine glands. One does not have to get very far

in his clinical observation to learn, for instance, that in hyperadrenia and hyperthyroidism, even very small doses of adrenal or thyroid will aggravate the symptoms. . . ."

Still another criticism comes to my attention as this Section is being completed. R. G. Hoskins, editor of *Endocrinology*, in a signed editorial entitled "What Is Endocrinology?" (*Endocrinology*, September, 1921, p. 610), after having dubbed me a "pseudoendocrinologist" and generally belittled my efforts, says: "The 'remarkable selective capacity of the organism' [quoting from me—H. R. H.] is, so far as can now be determined, a mere figment of the imagination, which is being grossly overworked as an excuse for haphazard, pluriglandular dosing. If the body cells were possessed of any such critical acumen as postulated, why should we ever encounter a case of acromegaly or hyperthyroidism? It is definitely proved that the cells will take up thyroxin or epinephrin in lethal quantities, when exposed to excess of these substances."

Now to discuss the last remark first: It is quite interesting to note that so prominent a writer as Solomon Solis Cohen, already quoted above, does not believe that this is quite so imaginary, and would you believe it, this very editor—R. G. Hoskins, of Columbus, Ohio—in commenting upon my original reprint sent to him toward the close of 1919 (the paper was published in the New York *Medical Record*, August 16, 1919) was good enough to write to me: "Thank you for your interesting reprint of your 'Hormone Hunger' paper. So far as I can see, it is perfectly good biology; it is rather demonstrated fact, however, than theory. You are somewhat too modest in applying it merely to hormones. Precisely the same mechanism—whatever it may be—comes into play when a young bone cell has to pick out calcium or an active muscle, glucose, from the blood. One can call it 'hunger,' 'specific affinity' or whatnot. Your term has the advantage of graphicness."*

Every theory has large opportunities for error to be woven in with it; otherwise, it would not be a theory but a fact. That I am aware of this is evident by the fact that I have called this a *hypothesis* of hormone hunger, and despite the reasonableness of the attitude of both Doctors Solis Cohen and Wood, they are not belittling the hormone

* From a personal communication received late in 1919, and shortly after its receipt, published in *The Organotherapeutic Review*, January 1920, p. 62.

hunger side of this matter so much as "hormone satiety," as I have called it.

However, we are not offering "lethal quantities" of any of these products; we are not discussing for the moment conditions of hypercrinism such as the hyperadrenia and hyperthyroidism referred to, we are talking about the capacity of the body to utilize certain hormones when it is presumed by the symptoms that these hormones are deficient; and I repeat that *clinical experience shows that in these persons the avidity with which the previously missing and artificially replaced substances are taken up, indicates that there must be some sort of a "hunger" as I call it, to facilitate their appropriation.* As to whether an excess is indeed permitted to remain in the circulation until oxidized or eliminated, is another matter, and just because we cannot be assured of this we should not cast the whole theory into the discard.

The fact remains that there *are* varying degrees of interest on the part of the various cells of the body for certain hormones that we may offer to them, and provided we are reasonable in the extent and character of our menus, we are going to accomplish a great many remarkable things with our "haphazard pluriglandular dosing" and the "impressionistic physiology" upon which it is based!

SECTION II. CHAPTER 6
DIAGNOSTIC ORGANOTHERAPY

One of the most interesting things about the administration of glandular extracts is the fact that we can learn in many instances, by the responsiveness of the patient to the product, points which are often of great diagnostic value.

As the student of endocrinology begins to look for certain clinical and laboratory findings to serve him as guides to the presence and character of certain endocrine disturbances, for absolute, infallible information he finds himself depending very largely upon the response of the individual to his treatment.

Clinical Diagnostic Therapeutics. My Thyroid Function Test, which is mentioned elsewhere in this book and which was developed from many clinical experiences with thyroid

therapy, some of which did not have altogether pleasant results, is an indicator of thyroid apathy or sensitiveness, as the case may be. In quite a number of cases, as a result of this test, the thyroid condition which it was desired to study has been ameliorated very much, or even has disappeared entirely during the test, and we were forced to conclude that the administration of the limited amount of thyroid given in the routine manner in order to secure the pulse chart expected in this test, was sufficient radically to change the conditions present. This in itself serves to prove to us that there was indeed a decided thyroid aspect to the case and that even the beginning of an indicated therapy sufficed to bring clinical changes in it, and consequently, proved its worth.

As we know, a great many circulatory, nervous and mental states frequently are related to disturbances of the ovarian function. At puberty, in connection with certain menstrual difficulties, and at the change of life, many an obscure symptom is discovered that cannot always be traced to a definite cause. Usually these symptoms are related to more or less prominent endocrine manifestations, and in the instance under discussion there is a change in the menses or associated manifestations. In many hundreds of cases, for lack of better knowledge and a more satisfactory procedure, it has been *presumed* that this or that difficulty might be related to the imbalance resulting from the disturbed ovarian function, *and, on treating this presumed dysovarism, many times the resulting nervous, circulatory or mental condition has been benefited simultaneously.* This has happened far too many times to be considered as coincidental, and many physicians have come to the conclusion that they may recommend organotherapy in cases of this kind with the expectation of acquiring diagnostic information of considerable value, in addition to the hoped-for therapeutic results.

If such an individual secures benefit from the organotherapy, in the realms controlled by the endocrine disturbance, and the benefit is extended to other physiological functions, which may or may not be related to those of the endocrines, and such experiences are repeated time and again, one very naturally comes to the conclusion that the organotherapy not merely rendered therapeutic service in suitable cases, *but also a diagnostic service,* the extent of which, and the value to the investigator, cannot very well be predicted in advance.

Experience With Epilepsy. The problem of the endocrine aspects of epilepsy, which is treated much more fully elsewhere, is mentioned by way of lending further emphasis to the matter under discussion. We do not know in advance that a given case has a definite endocrine disturbance of sufficient severity to be responsible for the difficulties which bring the patient to our notice. Yet, on the other hand, since the problem is so inherently difficult, and ordinarily is treated in a very unsatisfactory manner by the administration of sedatives of various kinds and the attempt to modify presumed underlying conditions such as toxemia, dietetic errors, etc., why is it not perfectly good practice to treat a case of epilepsy with an organotherapy which has been helpful in some other case, in the hope that the response to such organotherapy not merely may modify or cure the epilepsy but at the same time establish more firmly in our minds, or disprove, as the case may be, its presumed underlying endocrine aspects.

My personal experience has assured me in many cases that the response of the individual to an organotherapy often gives us diagnostic information of very considerable value, and with this in mind I cannot but feel even more justified in recommending a presumably indicated pluriglandular therapy, in a given case or class of cases, merely because, in the event that the results do not materialize within a reasonably long period of time, we can console ourselves that this aspect of the case is of minor importance and that we must look elsewhere to accomplish something for the patient.

Unfounded Criticism. I realize, of course, that this attitude of mine has been the cause of a good share of the criticisms advanced by those who feel that they must be thorough and accurate and sure of all the features of a condition before they treat the patient. But I have yet to find an ordinary physician or an endocrinologist who has made a special study of the subject, who can in advance determine an accurate endocrine diagnosis and apply thereto an accurate endocrine therapy. It happens that many of these scientists, who are ready to condemn me, admit, when pinned down, that they are almost as ignorant as the rest of us! And, in this connection, I cannot help adding that most of these critics pass their judgment and make their statements with little or no personal clinical experience from which to draw, a tendency by the way, which is customarily manifested towards "new ideas."

SECTION II, CHAPTER 7

ANAPHYLAXIS AND THE ENDOCRINES

The peculiar phenomenon known as anaphylaxis, or protein sensitization, becomes quite interesting to those physicians who make a persistent study of the internal secretions and organotherapy. Undoubtedly this reaction of the organism may have a much more intimate relationship to the ductless glands and their hormones than has been appreciated heretofore, and some personal observations may be related here to further an interest in the study and appreciation of the importance of this matter.

Protein poisoning, like any other toxemia, necessarily must invariably involve the detoxicating mechanism, and since this undoubtedly is presided over by the thyroid and allied endocrine glands, whenever we run across an individual who is sensitive to certain proteids, naturally we become interested in the functional capacity of these regulators of metabolism. For example, some physicians now believe that certain forms of high blood-pressure are examples of the anaphylaxis-like reaction of the body to certain protein toxins, and, if this is the case, the study and treatment of hypertension should involve the search for these poisons and their removal as far as possible, as well as the encouragement of the overburdened endocrine organs, or, on the other hand the encouragement of the opposing organs which maintain the so-called "hormone balance".

As we are confronted with individuals with peculiar sensitization to various foods, it is surprising how many of them also have some endocrine disturbance. The reverse is equally true. Asthma, which, to my way of thinking, many times is largely a matter of anaphylaxis, is very commonly associated with dyscrinism involving sometimes the thymus, sometimes the pituitary, and at other times the adrenals.

Anaphylaxis and Hypoadrenia. The influences that protein poisoning has upon the endocrine glands is of great importance. When an individual has an anaphylactic reaction he is virtually suffering from an acute protein poisoning, and, as in other poisonings with varied origins, one expects the natural defense of the body to poisons to be involved. Consequently there is a very large adrenal side

to conditions of this kind. We find that not infrequently hypoadrenia accompanies or follows anaphylaxis; and the regulation of this adrenal insufficiency often helps the "let down" resulting from the anaphylaxis. We also find occasional hints in therapeutic literature indicating that adrenal therapy, or, more correctly, adrenalin therapy, is used to modify or prevent the nitroid crises which accompany salvarsan injections (personally, I believe that the trouble is not entirely arsenical but rather the result of protein products broken up and released into the organism by the severe arsenic toxemia and a consequent protein poisoning plus arsenic poisoning). Again, adrenalin has been used with good success in urticaria which, as we know, is one of the manifestations of serum sickness, anaphylaxis, and other evidences of protein poisoning.

The condition known as status lymphaticus and its unfortunate outcome—thymus death—always has seemed to me akin to anaphylaxis, and if so, dyscrinism is once more related to this phenomenon for the thymus is believed to be an endocrine organ. The so-called "serum sickness" and the occasional deaths of children following serum treatment, seem to be in the same category and we know, at least, that some cases dying under these circumstances are found at autopsy to have had thymus enlargement, status lymphaticus and the disorganization resulting therefrom.

For some years I have been studying epilepsy from the standpoint of the ductless glands. Quite a good many hints in our experience indicate that there may be some anaphylactic aspect to the epileptic manifestations. For example: I recall a case where there was a bad post-abortion infection. The endocrine balance was very sadly deranged, and this individual from that time began to have increasingly severe epileptic seizures. It was believed that this particular epilepsy was a toxemia (and the consensus of opinion emphasizes the fact that if it is not exactly a condition of poisoning, it is very seriously aggravated by all forms of toxemia) either brought about by or aggravated by the dysovarism. Regulation of this condition not merely changed the obvious menstrual irregularities, but disposed of the associated epilepsy; in other words, there was reestablished a more nearly normal hormone balance favoring the disposal of the underlying condition of toxemia which is believed to be a factor in bringing about the epilepsy.

Hyperemesis Gravidarum an Anaphylaxis. Again: the matter of the nausea and vomiting of pregnancy may be considered from the standpoint of anaphylaxis. It is well known that the discomforts of the earlier months of pregnancy are due to a toxemia, and the attitude of those who believe that this toxemia is connected with the production by the placenta of certain protein substances to which the body reacts unfavorably, seems to have been substantiated by a good deal of clinical experience. But the interesting point is that when an individual who is presumed to be sensitive to these placental proteins is fed placenta substance, and an attempt is made to increase the immunity of the body to them, there shortly ensues in a generous percentage of cases a tolerance to the toxemia which puts an end to the vomiting no matter how serious it might have been. (It is interesting to note how frequently persons with an aggravated tendency to the toxemia of pregnancy will tell of difficulties that they have in connection with eating strawberries, or shell fish, or eggs, i. e., certain foods to which a very small minority is sensitive. The same is true in certain cases of asthma.)

Organotherapeutic Sensitiveness. In my experience with endocrine therapy I occasionally run across individuals whose clinical findings indicate the necessity for certain glandular remedies, and who, after such therapy has been inaugurated, react unfavorably to the extracts, and, despite every effort to cover up the product, find that they cannot take them at all. They are nauseated; they break out into a rash; they suffer from sympatheticotonus, i. e., their sympathetic system seems to be considerably more on edge than usual, and in many ways they discover that they react unfavorably to the remedy. Fortunately such individuals are few and far between. I have tried to get some figures, and imagine that perhaps 1:3000 is not far from correct. In other words, these individuals are like those unfortunates who cannot eat strawberries or in whom there is an unpleasant reaction to other special foods already mentioned, and, interestingly enough, often these persons with idiosyncrasies to glandular extracts, already have discovered a similar intolerance to other foods. I have repeatedly attempted to get around this difficulty, and while in some cases I have succeeded in increasing the tolerance, in others I have failed absolutely, merely because no matter how small the dose, or how apparently effectually it was hidden, the patients would immediately assure me that they

were having the same series of troubles which initiated the investigation along these lines.

A fertile field of study in protein sensitization and organotherapy is the development of a means whereby we can control those reactions of the body of an anaphylactic character which either are causing disease, as asthma, urticaria, nausea and vomiting, etc., or are interfering with our well-meant attempts to modify various dyscrinisms by means of the administration of organotherapeutic proteins.

Conclusions—The subject is still in a formative stage, but some suggestive conclusions may be made tentatively with advantage:

1. Protein metabolism is related to the internal secretions; hence disturbances in the routine of protein metabolism may be connected with a disturbed endocrine function;
2. Anaphylaxis, or protein sensitization, may involve the endocrine glands, and a part of the reaction connected with these idiosyncrasies may involve the ductless glands, especially the adrenals, thyroid, and in certain rarer instances, the thymus;
3. Hypoadrenia of anaphylactic origin needs to be treated like adrenal insufficiency of any other toxic origin; in other words, adrenal support is a reasonable measure in the case of anaphylaxis;
4. Occasionally, protein sensitization may be overcome by the establishment of an immunity, as is routinely done in the treatment of hydrophobia or the administration of bacterial vaccines. In vomiting of pregnancy, placenta substance administered over a period seems to favor an immunity to the placental proteins and a consequent control of the toxic irritability;
5. Occasionally organotherapeutic measures bring about an anaphylactic reaction, and this is particularly true in individuals already sensitive to other food proteins;
6. Whenever a clinical hint attracts attention to protein sensitization, the endocrines should be studied and brought into the matter both from the standpoint of diagnosis as well as treatment.

SECTION III.

PLURIGLANDULAR FORMULAS

A number of fundamental forms of pluriglandular therapy are represented by a series of formulas made in my laboratory of applied endocrinology. These formulas constitute a well-considered effort to apply the essential principles of organotherapy to several fairly large groups of cases. Each of these pluriglandular prescriptions has been used repeatedly, and it is with a confidence born of results—sometimes unexpected results—that they are recommended here.

The following statements embody the essential information regarding these stock formulas. In Section V, "Everyday Organotherapy," further consideration is given to various phases of the subject. Additional explanatory literature regarding several of these preparations is available on request, and the writer has accumulated a quantity of enthusiastic complimentary statements which are published from time to time, copies of which also will be sent to interested physicians.

The prescriber is advised to call for a full box of 100 doses since organotherapy is an attempt to reëstablish some function, and a few doses accomplish virtually nothing. It is desirable to specify "Harrower," at least until the pharmacist is acquainted with the products of this laboratory.

Attention is again called to the fact that no trade names are used, the formulas are neither secret nor ambiguous, and the labels contain no indications nor the boxes any explanatory circulars. In other words, every effort has been made to be as ethical and professional as possible.

NO. 1. ADRENO-SPERMIN CO.

ASTHENIA; Hypotension; Neurasthenia; Hypoadrenia; Run-down Conditions.

Formula: Each five grains represents the following combination: Adrenal substance (total) gr. ¼, Thyroid gland (U. S. P. IX) gr. 1/12, Spermin extract (from gonads) gr. 2 with Calcium Glycero-phosphate q. s.

Prescribe Thus: ℞ *Adreno-Spermin Co.* (*Harrower*) No. C. Sig. One, q. i. d. just before meals and at bedtime. (In acute cases and under special circumstances, one every three hours.)

Physiological Effects: A support to depleted adrenal function, hence a means of reducing neuro-muscular asthenia due to hypoadrenia. Favors sympathetic tone, stimulates oxidation, encourages cardiac activity, opposes circulatory stasis and increases "dynamos." An organotherapeutic tonic and reconstructant.

Indications: Chronic asthenic conditions with deficient oxidation (low urinary elimination) such as accompany chronic toxemia and follow acute infectious diseases, especially influenza, pneumonia, etc. The "fatigue syndrome" and run-down states with low blood pressure, cardio-circulatory insufficiency (cold extremities) and subnormal temperature. Many functional neuroses including neurasthenia, psychasthenia, melancholia, etc.

Remarks: Should be given early in acute conditions as a prophylactic against the expected "let-down," which is almost invariably an adrenal syndrome. Continue for 3 or 4 weeks, beginning with 1 every 3 hours, ending with 1, t. i. d. In chronic asthenias the blood pressure is an excellent guide both as to dosage and length of administration. A B. P. (systolic) of 110 mm. calls for 1, t.i.d., of 100 mm. 1, q.i.d. and 90 mm. or less 1, 5 or even 6 times a day. The longer the symptoms have persisted the larger the initial dose and the longer the treatment—up to 3 or more months.

Reference: Sec. IV, Ch. 5; Sec. V, Ch. 1, 2, 4, 17, 18; Sec. VI, Ch. 1, 2, 6, 9, 13, 16, 20, 24, 26.

NO. 2. ANTERO-PITUITARY CO.

DEFECTIVE CHILDREN; Maldevelopment; Infantilism; Cretinism; Epilepsy.

Formula: Each five grains represents the following combination: Pituitary gland (anterior lobe) gr. 2; Thymus gland, gr. 1; Thyroid gland (U. S. P. IX) gr. 1/12 with *Calcium Phosphorus Co.* (see No. 11) q. s.

Prescribe Thus: ℞ *Antero-Pituitary Co.* (*Harrower*) No. C. Sig. In children under five years one twice a day at meals, for 4 out of every 5 weeks. Continue for several months. (In larger children, and later in the treatment, an additional dose is advisable.)

Physiological Effects: A growth stimulant (morphogenic)

and endocrine regulator in defective development—hypoplasia—in children and youth. Found to have a favorable influence on *petit mal* and epilepsy for reasons not well defined, presumably due to a hypopituitaric factor in the etiology of these conditions.

Indications: Children with obvious endocrine deficiencies —thyroid, pituitary, etc. Retarded mentality (so-called "backward children" with or without decided stigmata), deficient growth, mongolism, dwarfism, etc. Epilepsy, *petit mal,* chorea and indefinite disorders which may be associated with or due to dyscrinism. As a means of broadening the use of thyroid in cretinism.

Remarks: Results have been both remarkable and unexpected, while, on the other hand, this formula has been often used in organic cases with definite cerebral defects with no benefit whatever. This cannot be determined in advance, so this treatment is often a "last straw" which is well worth trying. Must be given with the understanding that results are possible but not necessarily probable, and also that it is useless to give it for less than 4 to 6 months. Small doses—2 or 3 a day—for long periods are better than larger doses for a shorter time.

Reference: Sec. IV, Ch. 5, 7, 11, 12; Sec. VI, Ch. 4, 18, 21, 25.

NO. 3. PLACENTO-MAMMARY CO.

GALACTAGOGUE; Post-partum stimulant; Uterine involutant.

Formula: Each five grains represents the following combination: Desiccated placenta gr. 2, Mammary substance gr. 1½, Pituitary body (total) gr. 1/3 with *Calcium Phosphorus Co.* (*Harrower*) q. s.

Prescribe Thus: ℞ *Placento-Mammary Co.* (*Harrower*) No. C. Sig. Two at meals t. i. d. for first 10 days, thereafter one, t. i. d.

Physiological Effects: Mammary stimulant, galactagogue; post-partum regulator by favoring uterine involution. Beneficial influence upon infant's weight and nutrition.

Indications: Deficient or poor milk secretion, agalactia, hypogalactia. Infantile malnutrition. Preferably as a prophylactic especially in mothers whose previous nursing experiences were not good.

Remarks: Push the dosage for the first period, then reduce the dose until at three weeks or a month it may be

omitted. In some cases it has been given throughout the whole nursing period, since its omission caused a return of the hypogalactia within a few days. It has been noted that the use of this formula seems to inhibit menstruation during the nursing months, a distinct advantage both to mother and child.

Reference: Sec. IV, Ch.4; Sec. V, Ch. 8; Sec. VI, Ch. 31.

NO. 4. THYRO-OVARIAN CO.

DYSOVARISM; Amenorrhea; Dysmenorrhea; Neurasthenia; Menopause.

Formula: Each five grains represents the following combination: Ovarian substance (total) with Corpus luteum gr. 2½; Thyroid gland (U. S. P. IX) gr. 1/12; Pituitary body (total) gr. ⅛ with *Calcium Phosphorus Co.* (*Harrower*) q. s.

Prescribe Thus: ℞ *Thyro-Ovarian Co.* (*Harrower*) No. C. Sig. One, t. i. d., a. c. for 10 days, double dose for 7 to 10 days before menses, omit at onset of menses for 10 days. Repeat. (In total amenorrhea: 1, t. i. d. for 10 days, 2, t. i. d. for 2 weeks; omit a week; repeat.)

Physiological Effects: Ovaro-uterine regulator through the endocrine function of the ovaries and also the associated synergistic ductless glands.

Indications: Amenorrhea (delayed, scanty, absent or difficult menses); dysmenorrhea; sterility; sexual apathy; numerous neuroses and psychoses connected with the menstrual function. Epilepsy of the ovarian type (onset related to ovarian function or character aggravated in relation to periods). Climacteric disorders and circulatory imbalance of ovarian endocrine origin.

Remarks: This is one of the most efficient endocrine remedies. The fact that the associated endocrine glands are taken into consideration (for it may well be that the whole trouble is not so much ovarian as thyroid or pituitary, as both physiology and clinical experience have repeatedly shown) has made the use of this formula helpful when corpus luteum or ovarian substance alone had been tried previously for long periods without results. The cyclic method of administering suggested above is much more satisfactory than the usual signature, "one, three times a day."

Reference: Sec. IV, Ch. 8; Sec. V, Ch. 5, 6, 7; Sec. VI, Ch. 3, 12, 17.

NO. 5. HEPATO-SPLENIC CO.

INTESTINAL STASIS; Hepato-biliary Insufficiency; Alimentary Toxemia; Malnutrition.

Formula: Each five and a half grains represents the following combination: Hepatic parenchyma and desiccated spleen substance aa gr. 2, Spermin Extract gr. 1, Adrenal substance gr. ¼ and Thyroid (U. S. P.) gr. 1/20.

Prescribe Thus: ℞ *Hepato-Splenic Co.* (*Harrower*) No. 3. Sig. One after each meal and at bed time. (In certain instances the dose may be doubled and in any event dosage should be continued for weeks.)

Physiological Effects: Alimentary stimulant and regulator through the liver and spleen mechanism, as well as through the general endocrine system. A means of encouraging the secretory and detoxicative powers of the liver. Favors nutritive exchanges and has been known to stimulate large increases in weight.

Indications: Malnutrition of long-standing, toxic origin, especially in cachexia, tuberculosis, malaria, etc. Hepato-biliary insufficiency and sluggishness, resulting in intestinal stasis and toxemia.

Remarks: It seems that this organotherapeutic formula goes deeper than one expects of an ordinary hepatic stimulant. There is a support, a sort of physiological encouragement, which is more satisfactory than the usual "liver medicines." It should be remembered that this preparation exerts an educative influence and should be continued for some time, especially in the chronic cases of alimentary laziness.

Reference: Sec. V, Ch. 2, 22, 23.

NO. 6. PANCREAS CO.

SYMPATHETIC IRRITABILITY; Hyperthyroidism; Heart Hurry and Cardiac Weakness.

Formula: Each five grains represents the following combination: Adrenal and Pituitary glands (total) aa gr. ½, Ovarian substance gr. 1 and Pancreas gland (total) gr. 3.

Prescribe Thus: ℞ *Pancreas Co.* (*Harrower*) No. C. Sig. One, q. i. d., between meals. (In acute cases, especially in severe hyperthyroidism, the amount may be increased to 6 or 8 a day for a time.)

Physiological Effects: A cardiac muscular support and sedative. Functional antagonist to sympathetic irritability, especially that due to excessive thyroid secretion. Ovarian

content suggested by Crotti, since dysovarism is so common in such cases. (No objection to using same formula in men, however.)

Indications: Irritable, irregular, rapid and weak pulse, especially of endocrine origin. Nervousness and irritability resulting from hyperthyroidism. Post-influenzal and other toxic asthenias with a susceptible thyroid.

Remarks: A sympathetic sedative and useful remedy in hyperthyroidism, but with practically no direct influence upon the causative factors in this disease. Must be used with other measures, especially those calculated to antagonize or remove (1) sources of toxemia—teeth, tonsils, sinuses, colon, gall bladder, pelvis or elsewhere, (2) dyscrinism, especially disturbed functions of the ovaries or a persistent thymus or (3) emotional and psychic conditions which may and do unduly stimulate the thyroid and adrenal glands. An excellent means of preparing a case of toxic goitre for indicated surgery, and a worth-while remedy in severe toxemias where more radical measures are contra-indicated.

Reference: Sec. V, Ch. 10; Sec. VI, Ch. 5, 22, 23.

NOS. 7, 8, 9. THYROID CO. GR. ⅛, ¼, ½

HYPOTHYROIDISM; Myxedema; Cretinism; Minor Thyroid Insufficiencies.

Formula: Each five grains represents one eighth, one quarter or one half a grain of U. S. P. (IXth edition) Thyroid gland, respectively, with *Calcium Phosphorus Co.* q. s.

Prescribe Thus: ℞ *Thyroid Co.* (*Harrower*) gr. ⅛ (or ¼ or ½, as desired) No. C. Sig. One t. i. d. before meals.

(Note: In many instances a routine "step ladder dosage" is available, thus: For a week give one daily dose of No. 9, during the second week give 2 doses a day, during the third week 3 doses a day and during the fourth week 4 doses a day. Omit entirely during the fifth week; and, if necessary, repeat. This allows of the determination of the optimal dosage or tolerance by noting the response of the patient and with no harm whatever.)

Physiological Effects: Supplementary organotherapy in functional or organic thyroid secretory insufficiency. Remineralization. (See No. 11.)

Indications: Hypothyroidism—myxedema, with lesser forms of thyroid insufficiency, manifesting various degrees

of infiltration (of skin, mucous membrane and tissues generally), suboxidation, obesity, dermatoses or ovarian dystrophies. Cretinism, with maldevelopment, mental backwardness, mongolism, etc. In many nutritional disorders with metabolic insufficiency and defective elimination.

Remarks: The addition of the mineral salts to thyroid extract is based on sound reasoning, and clinical experience emphasizes its value. Thyroid extract is practically always given in the hope of increasing cell chemistry, for any degree of hypothyroidism, from the least to the most serious, always entails reduced metabolism and a consequent excessive production of acid wastes which automatically rob the organism of its alkaline reserve. This explains the acidosis and cellular poisoning which is the rule in thyroid insufficiencies, and at the same time supplements the thyroid gland stimulation by means of remineralization or restoring the alkaline mineral salts that have been depleted. Hence the excipient, used instead of milk sugar or starch, may be as therapeutically useful as the thyroid itself.

Reference: Sec. IV, Ch. 2, 3; Sec. V, Ch. 3, 13.

NO. 10. THYROID TESTING CAPSULES

THYROID TEST; Differential Diagnosis of Goitre; Estimation of Thyroid Secretion.

Formula: Each small box (of which there are three in each package) contains twelve graduated capsules of thyroid extract—four small, four medium and four large—representing one half, one and two grains of U. S. P. Thyroid, respectively.

Prescribe Thus: ℞ One Thyroid Test (Harrower), with chart. Sig. Follow printed instructions carefully.

Physiological Effects: A routine, graduated thyroid function stimulant, bringing about a reaction which varies in different individuals in proportion to the thyroid sensitiveness or apathy that is present, which may be recorded upon a simple, specially arranged pulse chart which serves for comparison between different cases, or the same case under different circumstances. A means of measuring thyroid functional activity.

Indications: In all forms of simple goitre and where thyroid enlargement is not obviously due to a well-established hyperthyroidism. As a differential diagnostic measure between goitre due to thyroid secretory incapacity or overstimulation. As a means of discovering a latent thyroid

sensitiveness without goitre. Also valuable in the study of metabolic dyscrasias, as obesity, rheumatism, etc.—where it is presumed that a thyroid element may be present, and where thyroid stimulation properly may be added to the treatment if the test shows the need for such treatment.

Remarks: A simple and extremely convenient measure—the physician has only to hand the package to the patient or prescribe it, as the instructions are minutely outlined with the chart which accompanies the test—which places thyroid medication upon a rational basis, instead of the administration of this remedy haphazard and until the patient complains of the untoward reaction due to overstimulation of the gland. Not alone useful in goitre and presumed thyroid troubles, but especially worth while in the study of disturbed cell chemistry, in ovarian disorders, in nutritional disturbances and in many cases where the discovery of thyroid irritability or apathy, as the case may be, would offer a new angle from which to consider and treat the case.

Reference: Sec. IV, Ch. 4, 12; Sec. V, Ch. 3, 18; Sec. VI, Ch. 3, 12 .

NO. 11. CALCIUM PHOSPHORUS CO.

DEMINERALIZATION; Hyperacidity (Acidosis or Acidemia); Toxemias.

Formula: Each tablet contains 15½ grains (one gram) of the following combination: One hundred parts represents Magnesium Phosphate 2, Calcium Phosphate (dibasic) and Calcium Glycerophosphate aa 8, Potassium Bicarbonate 32 and Sodium Bicarbonate q. s.

Prescribe Thus: ℞ *Calc. Phosphorus Co.* (*Harrower*) No. C. Sig. 3 tablets, crushed, with much water, twice a day, one hour before food.

Physiological Effects: Neutralizes systemic acid wastes. Replaces the alkaline mineral reserve, depleted by poor oxidation and abnormal production of acid or, at least, "alkaline robbing" products. This condition of mineral depletion is known in France as "demineralization" and the therapy as "remineralization."

Indications: Particularly useful in the adjunct treatment of chronic toxemic conditions, especially those so commonly associated with endocrine insufficiencies (notably of the thyroid gland). Indicated in a large list of chronic disorders in conjunction with gland feeding and other measures.

Remarks: The above formula (with the addition of sodium chloride) contains the mineral salts in the approximate proportions present in the blood, and is the standard excipient in The Harrower Laboratory. In many cases it is advisable to push the dosage for the first few weeks of the treatment with pluriglandular therapy and this non-glandular "mineral food" was added to the list since it is so commonly and definitely useful in these conditions. At least six grams a day should be given to an adult during the first two or three weeks of treatment, the dose then being reduced to, say, four grams every other day, or less often, depending upon the development of the conditions which may be present.

Reference: Sec. V, Ch. 2, 10, 18, 25; Sec. VI, Ch. 15.

NO. 12. AMYLO-TRYPSIN CO.

INDIGESTION; Flatulence; Gastric Dilatation, etc.

Formula: Each five grains represents the following combination: Amylopsin (pancreatic diastase) gr. ½, Pancreatin (U. S. P. IX) gr. 2½, Papain gr. ½, Berberine sulphate gr. 1/12 and a mixture of Cinnamon, Nutmeg and Jamaica Ginger, q. s.

Prescribe Thus: ℞ *Amylo-Trypsin Co.* (*Harrower*) No. C. Sig. Two, two hours after eating.

Physiological Effects: The first three ingredients further the digestion of proteid and starch, according to principles well established in physiological chemistry. Berberine is the yellow alkaloid of golden seal (and also the barberry) and is an efficient mucosal tonic; while the excipient consists of the well-known plant carminatives. A polyenzyme, tonic digestant formula.

Indications: Gastro-intestinal indigestion with achlorhydria, flatulence and fermentation. Wherever alimentary enzyme medication is called for, especially in atonic gastric insufficiency.

Remarks: The ferments are active and coöperate with one another. No pepsin is present but in its place papain (so-called "vegetable pepsin" which is active in either acid or alkaline media) is used. Each package contains a card on which is printed the following:

Note: The digestive ferments in this formula are destroyed by heat above 110 deg. F. It is advisable to take them some hours after eating, with water. Do not take with HOT foods or drinks.

NO. 13. HEMOGLOBIN CO.

ANEMIA; Chlorosis; Malnutrition.

Formula: Each six grains represents the following combination: Hemoglobin (repurified) gr. 4, Desiccated spleen parenchyma gr. 1, Acid Nucleinic (Nuclein) gr. ½ with *Calcium Phosphorus Co.* (*Harrower*) q. s.

Prescribe Thus: ℞ *Hemoglobin Co.* (*Harrower*) No. C. Sig. One before meals and on retiring. (Considerably increased doses may be given when marked hematinic effects are needed, say, three, four times a day for a week or more.)

Physiological Effects: Purveys an acceptable and easily absorbable iron to the organism. Non-constipating. Stimulates hematopoiesis. Encourages leucocyte production and phagocytosis.

Indications: All forms of anemia, both primary and secondary. Malnutrition due to blood conditions; convalescence from acute infectious diseases, surgery and the puerperium, especially where there has been a considerable loss of blood. Cachexia, cancer and chronic blood-destroying conditions including pernicious anemia. Where iron ordinarily is indicated.

Remarks: An unusually excellent combination which has been the means of causing a number of remarkable changes in the Hgb. index and blood picture. It should be stated that this or any other form of iron exerts no known influence upon the blood-cell-destroying factor in pernicious anemia. The French insist that hemoglobin, in addition to its hematinic virtues, also exerts a "homostimulant action" similar to the influence of thyroid extract upon thyroid secretion, etc. At all events, it is quite the best form of iron for oral administration.

Reference: Sec. V, Ch. 14.

NO. 14. NUCLEO-LECITHIN CO.

MALNUTRITION; Cachexia; Marasmus; Rickets, etc.

Formula: Each dose contains seven and a half grains (half a gram) of the following combination: Lecithin (90-95%) gr. 2½, Acid Nucleinic (Nuclein) gr. 1, Calcium glycerophosphate and Calcium phosphate (dibasic) aa gr. 2.

Prescribe Thus: ℞ *Nucleo-Lecithin Co.* (*Harrower*) grs. viiss, No. C. Sig. Three a day with food.
(Larger doses may be taken, say, up to two, four times a day.)

Physiological Effects: Each of the ingredients of this formula contains organic phosphorus in easily assimilable form; in fact lecithin is stated to be the richest and most easily acceptable form of organic phosphorus known. Each dose contains a generous amount of this product, as well as of nuclein and the glycerophosphate of calcium.

Indications: Malnutrition, especially in such chronic or developmental dystrophies as are known to respond particularly to phosphorus, including certain central nervous disorders, cachexia, marasmus and rickets. A reconstructive and nutritive nerve and cell tonic.

Remarks: Lecithin is a remarkable remedy and for many years has been warmly recommended for a very much longer list of disorders, mostly of a chronic and nerve type, than is mentioned above. The combination is as good a phosphorus bearing one as the writer knows of, and each individual element therein is generously dosed.

Reference: Sec. VI, Ch. 28.

NO. 15. SECRETIN CO.

INDIGESTION; Pancreatic and Biliary Insufficiency; Intestinal Toxemia.

Formula: Each five and a half grains represents the following combination: Secretin extract (duodenal) gr. 3, Bile salts (powdered) gr. 1½, Adrenal substance gr. ¼ with *Calcium Phosphorus Co.* (*Harrower*) q. s.

Prescribe Thus: ℞ *Secretin Co.* (*Harrower*) No. C. Sig. Two, between meals, t. i. d. It may be well to push the dosage to 3 or even 4 at a time for the first week or 10 days in intractable cases. In ordinary instances and to maintain the effects for a longer time in cases of long standing 1, t. i. d. may suffice.

Physiological Effects: Secretin stimulates pancreatic, biliary and intestinal glandular secretion, and actually forms a part of the finished enzymic products. Bile salts encourage increased biliary production. Adrenal substance is a tonic to unstriped muscle as well as to alimentary activity as a whole.

Indications: Chronic indigestion with toxemia, stasis, constipation and the numerous direct and indirect results thereof. Hepato-alimentary insufficiency with fetid, clay-like stools. Pancreatic insufficiency. Hypochlorhydria.

Remarks: Quite unlike the enzyme products commonly used in various forms of indigestion. Secretin is the nor-

mal, physiological hormone stimulus of practically all of the digestive secretions; it has been recommended for some years as an efficient and physiological remedy. In the digestive crises in summer complaints of children the contents of one half to one dose with food, t. i. d., is a useful dose. In the digestive disorders of tabes, pregnancy and cancer, especially the latter, where it will be recalled there is practically no HCl in the gastric secretion—and HCl is the natural excitant to secretin production in the duodenal mucosa—this formula is definitely indicated.

Reference: Sec. V, Ch. 22, 23, 24.

NO. 16. LIQUOR HYPOPHYSIS (U. S. P.)

PARTURITION; Hemorrhage; Shock; Stasis & Meteorism; Enuresis; Polyuria; Epilepsy; etc.; etc.

Formula: Each milliliter of the sterile, standardized solution of the active infundibular principle of the pituitary body, corresponds approximately to .02 gm. of the fresh gland.

Prescribe Thus: ℞ *Liq. Hypophysis* (*Harrower*) 15 mils. (½ oz.) (For physician's or hospital use only.)

Physiological Effects: Stimulant of unstriped muscle including heart, intestines, etc., and, especially, of the pregnant uterus. Homostimulant to the pituitary. Regulator of diuresis. Galactagogue.

Indications: As above and outlined later. As discussed previously under "Pituitary Body—Posterior Lobe."

Dosage: *Hypodermic*—Do not inject *superficially.* In Labor: Early (before dilation of the cervix) 2 minims, diluted. At completion of dilatation, 5-15 min. Repeat in 30 to 45 minutes, if needed. After Labor: Once daily for 2 to 4 days (antihemorrhagic, involutant, intestinal stimulant, galactagogue, diuretic!) In Surgery: 8-15 min. before operation, repeat (during long operations) after 2 hours, otherwise at each of three intervals of 6 to 8 hours. (To prevent shock, hemorrhage, meteorism, etc.) In Nose and Throat Surgery: 5-15 min. one hour prior to tonsillectomy, etc. (5-8 min. in children) prevents hemorrhage and shock. In Cardiac Asthenia and Failure: 5-8 min. daily or more often. In Graves' Disease: 5-10 min. twice daily; later once daily and still later once every other day. In Intestinal Paresis: (with stasis, alimentary cramps and meteorism) 15 min., repeat in 3 or 4 hours, if needed. In Obstipation: 5 min.; after 2 hours, 10 min.; after 4 hours

more, 15 min.; after still another 4 hours, 15 min., if needed. (Give to effect.) In Enuresis: 5-8 min. every other day for 2 weeks; double this dose to adults. In Epilepsy: 10-15 min. (less in children) daily, or every other day for several weeks, followed later, perhaps, by 15 min. once a week for some months in conjunction with *Antero-Pituitary Co.* (*Harrower*) (No. 2, q. v.) In Diabetes Insipidus: 10-15 min. daily or every other day for 8 or 10 doses.

Oral Administration. Twice the stated hypodermic dose, twice or three times a day, in the chronic phases of conditions mentioned above, as: Before surgery, in cardiac disease, Graves' disease, alimentary stasis and atony, enuresis and epilepsy. Useless *per os* in labor, shock, severe obstipation and active conditions where immediate results are necessary.

Intravenous Injection. In serious collapse, cardiac failure, hemorrhage and where the indicated hypodermic use is ineffective, give 15-30 min. (1 or 2 mils.) with 20 mils. or more of sterile saline solution into the medium basilic vein. Repeat in 2 hours, if desirable.

Remarks: "A very wonderful and unexcelled remedy in a surprisingly large and varied list of disorders."

The physiological efficacy of this preparation is rigidly standardized in harmony with the requirements of the U. S. P. IX and the recommendations of the Treasury Department of the U. S. In addition to careful checking in the laboratory, a portion of each batch is sent East for restandardization in a prominent research laboratory. It is stable, sterile and standard. The vial package developed in The Harrower Laboratory favors rapidity of use, convenience in securing smaller or larger doses than the usual ampule contents and, hence, economy.

Instructions: Remove vial from protecting box. Bare the rubber covering. Alcoholize this and the sterile needle. Dry thoroughly. Insert needle through rubber. Invert. Withdraw *just enough* of the solution—*DO NOT RETURN ANY EXCESS.* Replace cover. Return to container.

NO. 18. IODIZED THYROID CO.

GOITRE; Simple Thyroid Enlargement; Hypothyroidism.

Formula: Each six grains represents the following combination: Thyroid gland (U. S. P. IX), Ferrous Iodide, Acid Nucleinic (Nuclein) aa gr. ¼ with *Calcium Phosphorus Co.* q. s.

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Prescribe Thus: ℞ *Iodized Thyroid Co.* (*Harrower*) No. C. Sig. One, t. i. d. between meals with water. (Occasionally it may be best to give four to six a day for a short time.)

Physiological Effects. Replaces the deficient thyroid hormone, stimulates thyroid secretory activity. The iodine is a thyroid stimulant (food) and nucleinic acid reënforces the whole by furthering the immunity and leucocytic functions.

Indications: Simple goitre or enlargement of the thyroid with no evidence of thyroidism (best to have previously made a Thyroid Function Test—see No. 10—and differentiated between thyroid enlargement due to glandular insufficiency and that due to glandular irritability); anemia and malnutrition, especially in girls at puberty who have slight enlargement of the thyroid; hypothyroidism with or without enlargement of the gland.

Remarks: Where thyroid enlargement is due to an attempt of the body to meet certain unusual demands for the thyroid stimuli, the gland is enlarged to render the larger service demanded of it. This is also true where there is a thyroid cellular inefficiency with the usual demands of the organism for its influence on metabolism. In girls at puberty and women during the various ovarian changes there often appears an enlargement of the thyroid which is benefited by such treatment as is represented by this special formula. It serves the double purpose of offering a suitable dose of thyroid and a convenient form of iodine (which, by the way, has the added advantage of the hematinic value of the iodide of iron) plus the leucocyte and resistance-stimulating effect of nuclein.

Reference: Sec. IV, Ch. 4; Sec. V, Ch. 28; Sec. VI, Ch. 12, 35.

NO. 22. BILE SALTS CO.

BILIARY INSUFFICIENCY; Mucous Colitis; Constipation; Intestinal Indigestion.

Formula: Each dose represents three grains each of repurified powdered bile salts and desiccated hepatic substance.

Prescribe Thus: ℞ *Bile Salts Co.* (*Harrower*) No. C. Sig. One q. i. d. between meals for 3 days, then double dose for 3 more days, then treble dose for 3 days, continue until free bile appears with stool, then reduce to 3 a day for some weeks. (It is well to repeat this step-ladder routine

monthly, especially in old and stubborn cases.) Note: It is best to give written instructions to the patient direct as the dose varies naturally with the hepato-biliary response and the above routine is infinitely superior to the usual method; therefore I suggest this direction to the pharmacist: Sig. Take increasing doses between meals as directed.

Physiological Effects: Hepato-biliary stimulant, increasing both the flow of the bile and the general hepatic activity including its detoxicative functions. Favors the reëstablishing of normal conditions in muco-membranous enterocolitis.

Indications: Functional liver insufficiency, intestinal stasis, sluggish bile flow, gall stones, duodenal indigestion and chronic nutritional disorders such as tuberculosis where hepato-biliary function is especially important. Mucous colitis. Chronic hepatic disease with cirrhosis or hypertrophy.

Remarks: The clinical value of bile is not appreciated enough. It is the cholagogue *par excellence.* Hepatic substance has been used for years in France to facilitate the reëstablishment of deficient liver activity. The above combination is superior to either of the ingredients.

The proper dosage is "enough." If constipation is marked and the patient is taking cathartics, continue them as before. Suggest the above step-ladder dosage and when free bile is seen omit the cathartics, continuing the high dosage of the *Bile Salts Co.* (*Harrower*) for two or three days and gradually reduce it, until, perhaps, just 2 or 3 are taken at night. In chronic, toxic cases I recommend the repetition of this routine several times and the continuance of this treatment for months.

In France Prof. Roger insists that mucous colitis is largely a disorder due to biliary sluggishness and explains his reasons very satisfactorily:

Reference: Sec. V, Ch. 22, 23.

NO. 23. PANCREATIN-BILE CO.

INTESTINAL INDIGESTION; Biliary Insufficiency; etc.

Formula: Each dose represents two grains each of Pancreatin (U. S. P. IX), Bile salts and Hepatic substance (as in No. 22).

Prescribe Thus: ℞ *Pancreatin-Bile Co.* (*Harrower*) No. C. Sig. Two an hour or more after each meal. (Later this may be given in smaller doses or after two main meals.)

Physiological Effects: Digestant, hepato-biliary regulator and general alimentary secretory stimulant.

Indications: Intestinal indigestion with hepato-biliary torpor, alimentary toxemia and stasis. Essentially the same indications as suggested for No. 22.

Remarks: Perhaps the addition of the pancreatin makes the combination more suited for the control of conditions in which the intestinal rather than the hepatic element predominates, especially where the stools are malodorous and often light colored and sticky.

NO. 24. PARATHYROID CO.

PARALYSIS AGITANS; Tetany; Hypoparathyroidism.

Formula: Each five grains represents the following combination: Desiccated Parathyroid glands gr. 1/20, Spermin Extract (from interstitial cells of Leydig) gr. 1, Bile salts (powdered) gr. 1½ with *Calcium Phosphorus Co.* (*Harrower*) q. s.

Prescribe Thus: ℞ *Parathyroid Co.* (*Harrower*) No. C Sig. One, four times a day between meals.

Physiological Effects: Stimulates the detoxicative influence of the parathyroids (which are said to have the faculty of destroying poisons which have a predilection for the nervous system); increases muscular tone and stimulates hepato-biliary activity.

Indications: Parathyroid insufficiency, including certain neuro-muscular disorders as paralysis agitans, tetany and chorea.

Remarks: Parathyroidism therapy has been frequently recommended in paralysis agitans and undoubtedly it has been helpful in many cases, but I do not urge it with the enthusiasm that I recommend many other formulas from this laboratory. At least this formula is superior to parathyroid alone for two reasons: (1) There is a well-established functional relation between the liver and parathyroids and in paralysis agitans there is invariably need for hepato-biliary stimulation, (2) the cellulo-tonic effect of spermin is useful in all cases of waning glandular activity, senility and deficient oxidation.

The treatment must be given for many months, and it would be better not to start than to give a couple of hundred 5-gr. doses alone. Sometimes double the above dosage for one out of every three weeks is an advantage.

Reference: Sec. IV, Ch. 10; Sec. VI, Ch. 30.

NO. 26. ADRENO-HYPOPHYSIS CO.

ASTHMA; Bronchial Asthma.

Formula: Each five grains represents the following combination: Adrenal substance (total) gr. ½, Pituitary gland (anterior lobe) gr. 2, Calcium Lactate and Calcium Phosphate (dibasic) aa q. s.

Prescribe Thus: ℞ *Adreno-Hypophysis Co.* (*Harrower*) No. C. Sig. One q. i. d. before meals and at bedtime. (Occasionally a larger dose may be given, say, one every three hours or two, t. i. d.)

Physiological Effects: Antagonizes asthenia and hypoadrenia; is said to exert a beneficial effect (both because of the adrenal, pituitary and calcium content) on bronchial asthma and allied conditions.

Indications: Asthma and bronchial asthma in children and adults, especially where there may be an underlying endocrine element present.

Remarks: This formula is still purely experimental. It has prospects of real value. The dosage suggested is innocuous and is not known to cause unpleasant reactions. Such a preparation cannot take the place of antispasmodic remedies like morphin or adrenalin, which may have to be used simultaneously. This remedy, however, may make some favorable modification of the underlying cause of the asthma. It is at least worth trying in suitable cases, in conjunction with other indicated measures.

Reference: Sec. V, Ch. 16, 26.

NO. 29. THYRO-PANCREAS CO. with SPERMIN
NO. 30. THYRO-PANCREAS CO. with OVARY

FUNCTIONAL HYPERTENSION

Formulas: Each five grains represents the following combinations: Pancreas gland (total) gr. 2, Thyroid gland (U. S. P.) gr. 1/12, Spermin extract (or Ovarian substance, respectively) gr. 2 with *Calcium Phosphorus Co.* (*Harrower*) q. s.

Prescribe Thus: ℞ *Thyro-Pancreas Co.w. Spermin* (*or Ovary*) (*Harrower*) No. C. Sig. One q. i. d., at meals and bedtime.

Physiological Effects: Antagonist to adrenal irritability and functional irritation of blood-pressure regulating mechanism, stimulant of oxidation and regulator of gonad function. In the male the spermin acts by stimulating cell activ-

ity, while in the female the ovarian substance is helpful by regulating ovarian endocrine function, especially at or after the menopause.

Indications: High blood-pressure where it is evident that the sole cause is not renal, cardiac or vascular (arteriosclerosis).

Remarks: Numerous clinical tests checked by careful sphygmomanometry have proved that the use of these formulas does reduce functionally high tensions. In organic hypertension there may be a functional element as well as the structural change. Here this treatment may be given with the prospect of causing some slight reduction in that part of the tension which may be functional. If it is given for a month or six weeks with no measurable benefit, it is not likely that it would be beneficial to continue its use.

References: Sec. V, Ch. 15; Sec. VI, Ch. 34.

NO. 38. MAMMA-OVARY CO.

DYSOVARISM; Menorrhagia; Prolonged Menses.

Formula: Each five grains represents the following combination: Mammary substance gr. 2½, Ovarian substance gr. 1, Thyroid gland gr. ⅛ with *Calcium Phosphorus Co.* (*Harrower*) *q. s.*

Prescribe Thus: ℞ *Mamma-Ovary Co.* (*Harrower*) No. C. Sig. One t. i. d., a. c., double 3 days before and during menses, omit for one week. Repeat.

Physiological Effects: Ovarian regulator, antagonist to excessive ovarian endocrine function.

Indications: Moderate menorrhagia with or without dysmenorrhea; difficult menstrual onset; too frequent menses or prolonged menses; dysovarism with a tendency to ovarian irritability and pelvic congestion. Used in preference to No. 40 (q. v.) in girls and young women with functionally hyperactive ovaries with an excessive or prolonged flow, etc.

Remarks: The best results from this formula are obtained when it is pushed just before and during the flow. In disturbed ovarian functioning sometimes this formula may be alternated with *Thyro-Ovarian Co.* (*Harrower*) or may replace it in ovaro-uterine conditions which lean toward menorrhagia in which the results from this latter formula leave something to be desired.

Reference: Sec. IV, Ch. 8; Sec. V, Ch. 9; Sec. VI, Ch. 8, 10.

NO. 40. MAMMA-PITUITARY CO.

MENORRHAGIA; Metrorrhagia; Uterine Subinvolution; Fibroids; etc.

Formula: Each five grains represents the following combination: Mammary substance gr. 2½, Ergotin (Bonjean) gr. ½, Pituitary gland (total) gr. ¼ with *Calcium Phosphorus Co.* (*Harrower*) q. s.

Prescribe Thus: ℞ *Mamma-Pituitary Co.* (*Harrower*) No. C. Sig. One, t.i.d., a.c., double 3 days before and during flow, omit for one week. Repeat. (Occasionally more may be given during the heaviest part of the flow, say, 2 every three hours.)

Physiological Effects: Antagonist to ovarian endocrine function; uterine muscular tonic; uterine circulatory depletant.

Indications: Menorrhagia, metrorrhagia and prolonged or excessive menstrual or climacteric uterine hemorrhages. Uterine fibroids.

Remarks: The above formula has been used with benefit in organic uterine disease, seemingly permanent in fibromata and temporary in cancer. The chief benefit is shown by the controlled bleeding, though quite often a fibroid will be materially reduced in size. When given for the uterine oozing of cancer, an explanation should be made that the expected benefit is symptomatic. In menorrhagia of ovarian origin this is not merely a symptomatic regulator of the excessive flow, but it is simultaneously modifying the underlying conditions responsible for the hemorrhage.

Reference: Sec. V, Ch. 9; Sec. VI, Ch. 8, 10.

NO. 41. LEYDIG CELL CO.

PROSTATIC HYPERTROPHY; Impotence; Hypogonadism.

Formula: Each five grains represents the following combination: Spermin extract (from the interstitial cells of Leydig) gr. 2½, Thyroid gland (U. S. P.) gr. 1/16 with Calcium Glycerophosphate and *Calcium Phosphorus Co.* aa q. s.

Prescribe Thus: ℞ *Leydig Cell Co.* (*Harrower*) No. C. Sig. One q.i.d., a.c.

Physiological Effects: Homostimulant of gonads and the essential endocrine function of these glands; antagonist to functional prostatic hypertrophy. Cell stimulant in impotence and senility.

Indications: Prostatic hypertrophy not due to present infection or adenoma; prostatic hyperesthesia; asthenia of gonad origin; impotence and deficient gonad function; senility.

Remarks: Originally prepared for the experimental control of simple prostatic hypertrophy on the assumption that when gonad function is on the wane the prostate may take up certain of its endocrine functions vicariously and become enlarged in a compensatory fashion. Results seem to have established its value, reduced prostatic hyperesthesia, lessened micturition and a general feeling of well-being having followed the use of the formula for a month or six weeks.

Reference: Sec. V, Ch. 20; Sec. VI, Ch. 11.

NO. 43. LYMPHATIC CO.

LYMPHATISM; Hemophilia; Malnutrition; etc.

Formula: Each six grains represents the following combination: Desiccated lymphatic glands gr. 2, Spleen substance gr. 1½, Thyroid gland (U. S. P.) gr. 1/16 with Calcium lactate q.s.

Prescribe Thus: ℞ *Lymphatic Co.* (*Harrower*) No. C. Sig. Two, with food, t.i.d. Dose may be reduced after 10 days or more; and should be continued for fully a month.

Physiological Effects: Alterative and reconstructant in lymphatic conditions; stimulant of the coagulative capacity of the blood; cellular constructant.

Indications: Badly nourished, anemic children with a tendency toward hemorrhage, especially in those with large and recurrent adenoids, hypertrophied tonsils, etc. Certain forms of hyperthyroidism, with or without additional doses of thyroid gland. Lymphatic enlargement.

Remarks: Used chiefly for children, though not contraindicated in adults of the lymphatic, "bleeder" type. May be given to such for a week or more before an anticipated operation (give an injection of *Liq. Hypophysis U. S. P.* —*Harrower*—half an hour before operation, also.)

NO. 47. PITUITARY CO.

HYPOPITUITARISM; Infantilism; Hypogonadism.

Formula: Each dose represents Pituitary gland (total), and Pituitary gland (anterior lobe) aa gr. 1½ with *Calcium Phosphorus Co.* q. s.

Prescribe Thus: ℞ *Pituitary Co.* (*Harrower*) No. C.

Sig. One q. i. d., a. c.

Physiological Effects: Stimulates carbohydrate metabolism; increases cellular growth and encourages gonad function, especially in essential pituitary dysfunction.

Indications: The adiposo-genital syndrome of Fröhlich; hypopituitarism; infantilism; eunuchoidism; maldevelopment of gonads (hypogonadism); developmental dystrophies of pituitary origin.

Remarks: Contains a greater proportion of the active glandular portion of the pituitary gland (the anterior lobe) than pituitary gland alone, hence is more useful in hypopituitarism, which is essentially an anterior lobe disease, than total gland products. Above figures refer to finished desiccated gland and not to fresh substance.

NO. 48. PROSTATE CO.

PROSTATIC DISEASE; Prostatic Neurasthenia; Hypertrophied Prostate; etc.

Formula: Each six grains represents the following combination: Prostate gland (desiccated), Spermin extract (from interstitial cells of Leydig) and Lymphatic glands, aa gr. 1½, Acid Nucleinic gr. ⅛ with *Calcium Phosphorus Co.* (*Harrower*) q. s.

Prescribe Thus: ℞ *Prostate Co.* (*Harrower*) No. C. Sig. One t. i. d., a. c. (Occasionally considerable increases in this dosage are helpful. It is also advisable to continue the treatment for several months, in which case I suggest its omission every fifth week.)

Physiological Effects: Homostimulant to prostate and sex glands; antagonist to prostatic irritability.

Indications: Latent prostatic insufficiency with or without an old posterior urethral or prostatic infection; prostatorrhea; endocrine insufficiency of the gonads with impotence, relative or actual. Prostatic hypertrophy. Prostatic neurasthenia and following prostatectomy. Senility.

Remarks: Of similar character to No. 70, *Gonad Co.* (*Harrower*) q. v.

Reference: Sec. V, Ch. 4, 20; Sec. VI, Ch. 2.

NO. 49. PLACENTA CO.

VOMITING OF PREGNANCY; Nausea of Pregnancy; Placental Toxemia.

Formula: Each six grains represents the following combination: Placental parenchyma (desiccated) gr. 5, Thy-

roid gland (U. S. P.) gr. 1/24 with *Calcium Phosphorus Co.* (*Harrower*) q. s.

Prescribe Thus: ℞ *Placenta Co.* (*Harrower*) No. L. Sig. Two with charged water or ice, q. i. d.

Physiological Effects: Antagonizes placental toxemia and sedates hyperemesis gravidarum. Presumed to act by artificially establishing an immunity to the placental protein poisons to which certain individuals are unusually sensitive.

Indications: Vomiting and nausea of pregnancy.

Remarks: Often a last resort remedy of unusual efficacy when all other treatment has failed. Give by mouth with or without sedative medication. Morphin has been necessary to allow absorption. Give at times and under circumstances which will favor retention. Twenty-five grains a day for ten days, is usually a complete treatment since the expected results will come before this time if the measure is going to be efficacious. Continue for a longer time if evident benefit has been initiated.

Reference: Sec. VI, Ch. 6, 7, 27.

NO. 57. THYMUS-SPERMIN CO.

ARTHRITIS; Arthritis Deformans; Chronic Rheumatism; Asthenia.

Formula: Each six grains represents the following combination: *Adreno-Spermin Co.* (*Harrower*) and Thymus gland aa. gr. 3.

Prescribe Thus: ℞ *Thymus-Spermin Co.* (*Harrower*) No. C. Sig. One, q. i. d., p. c. (Occasionally given in larger doses for a few weeks, then reduced to the above.)

Physiological Effects: Stimulates metabolism, antagonizes adrenal apathy and asthenia. (See No. 1 *Adreno-Spermin Co.—Harrower*). According to Nathan and others desiccated thymus is effective in certain chronic arthrites, including arthritis deformans.

Indications: Chronic arthritis or rheumatism with poor metabolism and deficient cellular elimination. Arthritis deformans.

Remarks: Each of the ingredients of this formula, the *Adreno-Spermin Co.* (*Harrower*) and desiccated thymus have rendered service in arthritis deformans. In many cases the prospects for results are not bright, though this treatment has been used without hope and as a last resort with results which were a pleasant surprise to all concerned. It must be given persistently. It may be well to modify

the dosage by starting with the routine dosage suggested above, for a month, then omit one week and then take 2, q. i. d. for a month, then omit for a full month, then repeat this routine, taking note of any slight changes during these different periods. Only a part of the routine treatment.

Reference: Sec. V, Ch. 18.

NO. 68. SPERMIN-HEMOGLOBIN CO.

ASTHENIC ANEMIA; Hypoadrenia; Malnutrition.

Formula: Each six grains represents the following combination: *Adreno-Spermin Co.* (*Harrower*) (Stock Formula No. 1, q. v.) and Repurified Hemoglobin, aa gr. 3.

Prescribe Thus: ℞ *Spermin-Hemoglobin Co.* (*Harrower*) No. C. Sig. One, q. i. d., a. c.

Physiological Effects: Support to depleted adrenal function. Increases sympathetic tone, increases oxidation and "dynamos" (see Formula No. 1). Hematinic reconstructant.

Indications: Conditions of asthenia due to hypoadrenia with which anemia and malnutrition are present. Low blood-pressure with anemia. Following operations and experiences which have depleted both the adrenal function and the blood.

Remarks: This formula is essentially the Adreno-Spermin formula to which attention has already been called, plus the effective hematinic, hemoglobin. *Spermin-Hemoglobin Co.* (*Harrower*) takes the place of the combined administration of No. 1 (*Adreno-Spermin Co.*) and No. 13 (*Hemoglobin Co.*), to which attention has already been called.

Reference: Sec. V, Ch. 14.

No. 70. GONAD CO.

IMPOTENCE; Asexualism; Hypogonadism.

Formula: Each six grains represents the following combination: Adrenal gland (total) gr. ¼, Thyroid gland (U. S. P.) gr. 1/12, Pituitary gland (anterior lobe) gr. 1, Prostate gland and Spermin extract (from Leydig cells) aa gr. 1½ with *Calcium Phosphorus Co.* (*Harrower*), q. s.

Prescribe Thus: ℞ *Gonad Co.* (*Harrower*) No. C. Sig. One q. i. d., a. c. (Note: From 3 to 8 may be given daily.)

Physiological Effects: General cell stimulant, especially of the essential sex glands through the pituitary, adrenals, thyroid and gonads themselves. The addition of the anterior pituitary seems to be especially helpful (recall that the dys-

trophia adiposo-genitalis—hypopituitarism—is a functional genital disorder which has been benefited by suitable organotherapy). Antagonizes asthenia. Stimulates prostato-gonad function on the principle of homostimulation.

Indications: Functional and endocrine impotence; asexualism both organic and acquired; senility; presenility; hypogonadism; sexual neurasthenia; aspermia; sterility.

Remarks: Best given in step-ladder dosage, as 1, t.i.d. for several weeks, then 2, t.i.d. for a longer period, followed, if necessary, by another period when even 3, t.i.d. may be taken. Given in conjunction with associated treatment. Has no effect upon conditions with a psychic basis, nor does it influence latent infections. Not rapid in its action, therefore unusual caution must be taken to urge protracted use or not to start it.

Reference: Sec. V, Ch. 20, 21.

No. 73. GONAD-OVARIAN CO.

STERILITY; Hypo-ovarism; Asexualism; Infantilism; Amenorrhea.

Formula: Each six grains represents the following combination: *Thyro-Ovarian Co.* (*Harrower*) (No. 4, q. v.) gr. 3, Spermin extract and pituitary gland (anterior lobe) aa gr. 1½.

Prescribe Thus: ℞ *Gonad-Ovarian Co.* (*Harrower*) No. C. Sig. One q. i. d., a. c. If the patient is menstruating or there is a molimen, prescribe as formula No. 4, i. e., 1, t.i.d., a. c. for 10 days, double dose for 7 to 10 days before menses (or molimen), omit at onset of menses for a week. Repeat.

Physiological Effects: Ovarian stimulant through the endocrine function of the ovaries plus the gonado-stimulant effect of the anterior pituitary and the general sex and cell stimulant effect of spermin from the male gonads.

Indications: Prolonged amenorrhea; infantilism; sex mal-development and hypofunction; lack of libido; endocrine sterility; and, in general, the same indications as *Thyro-Ovarian Co.* (*Harrower*) (q. v.) save that the condition is more decisive and marked. Where the use of this latter has not been sufficiently stimulating enough.

Remarks: Endocrine stimulation through all of the glands involved in "the sex complex" is about the only physiological hope in many cases of essential amenorrhea and sexual apathy in the woman. The cyclic method is better if it can be applied. Here, also, the gland feeding must

be continued with persistence for long periods because the attempt is being made to reëducate certain endocrine functions, which naturally takes months and, further, the time that the ovaries are especially stimulable only lasts a comparatively short time each month.

Reference: Sec. IV, Ch. 8; Sec. V, Ch. 6, 7.

No. 79. ADRENO-OVARIAN CO.

DYSOVARISM with Hypoadrenia.

Formula: Each dose represents five grains of the *Thyro-Ovarian Co.* (*Harrower*) with Adrenal substance (total) gr. ¼.

Prescribe Thus: ℞ *Adreno-Ovarian Co.* (*Harrower*) No. C. Sig. One, t. i. d. for 10 days, double dose for 7 to 10 days before menses, omit at onset for 10 days. Repeat.

Physiological Effects: Ovaro-uterine regulator through the ovarian hormone function, plus adrenal support.

Indications: Ovarian dysfunction, amenorrhea, dysmenorrhea and, generally conditions in which the *Thyro-Ovarian Co.* (*Harrower*) would be used (see No. 4) with hypoadrenia and asthenia, low blood-pressure and general cellular apathy.

Remarks: Supplements the well-known Thyro-Ovarian formula with adrenal support and obviates the occasional necessity for prescribing *Adreno-Spermin Co.* (*Harrower*) with the ovarian treatment. Especially helpful in pallid, asthenic girls and young women with ovarian insufficiency, amenorrhea, etc. Also indicated in the climacteric when the dysovarism is complicated with an aggravated fatigue syndrome, etc.

Reference: Sec. IV, Ch. 8; Sec. V, Ch. 5, 6, 7; Sec. VI, Ch. 3, 12, 17.

No. 85. CAPS. RENAL CO.

NEPHRITIS; Albuminuria; Renal Insufficiency.

Formula: Each dose represents desiccated renal glomerular tissue and desiccated pancreas gland, aa gr. 2½.

Prescribe Thus: ℞ *Renal Co.* (*Harrower*) No. C. Sig. One, q. i. d., a. c.

Physiological Effects: Tends to reduce renal impermeability; lessens albumin elimination through the glomeruli; stimulates renal efficacy; encourages pancreatic and intestinal physiology.

Indications: Acute and chronic Bright's disease with or without albuminuria; essential albuminuria without other renal (or local) findings; deficient renal activity with polyuria and low total solids.

Remarks: For years renal glomerular substance has been recommended, especially in France, for nephritis and albuminuria. Various explanations have been given as to why it is useful. Suffice it to say that many times it has reduced the urinary difficulties, both clinical and laboratory, of various forms of nephritis. The addition of pancreas gland is rational, for it tends to reduce the very conditions which are aggravating to the renal cells, as well as to neutralize the adrenal irritability so usual in such cases.

Reference: Sec. V, Ch. 26.

SECTION IV

THE DIAGNOSIS OF THE INTERNAL SECRETORY DISORDERS

There is no convenient source of information on this subject. Among the several books on endocrinology—notably Sajous, Biedl, Falta-Myers, Carnot and Pende the whole subject is considered, but chiefly from the standpoint of the well-defined, structural endocrine disorders. To my own way of thinking the functional endocrinopathies far outweigh in importance the text-book diseases of this character because they are so much more frequent, and so much more routinely overlooked.

This section contains a large amount of data on the diagnostics of endocrine disorders in general practice, and is not intended to be either complete or technical, but rather to serve as a means of reminding the reader—presumably "an ordinary doctor" like myself—of some points which may be really helpful in the day's work.

SECTION IV. CHAPTER 1

THE FREQUENCY OF INTERNAL SECRETORY DISORDERS IN GENERAL PRACTICE

The insidiousness and practical importance of disturbed function of the glands of internal secretion is far greater than most physicians realize; and the frequency with which it may be encountered in almost every phase of general as well as special practice, coupled with the fact that many times it is entirely overlooked, constitute the occasion for this section on endocrine diagnosis.

The Broad Influence of the Hormones. Increasing attention is being paid to the study of the glands of internal secretion, or endocrine organs, as we shall call them, and rightly so. Our knowledge of the physiological action of these organs has been acquired almost entirely in the last fifty years; and has been augmented very materially in the past 15 or 20 years. In fact, practically all we know of the internal secretions has been learned in this brief period and the establishment of the fundamental contentions of the now

famous French scientist, Claude Bernard and Brown-Séquard, were not accomplished and their experiences scientifically explained until as recently as 1902, when Professor E. H. Starling, of University College, London, suggested the term "hormone" (from the Greek word which means "I arouse" or "I set in motion") to designate a class of chemical substances, of which his newly discovered secretin was the type (see Sec. V, Chap. 15). These hormones are produced in various parts of the body and are carried by the blood or other body fluids to various more or less remote organs where they excite certain physiological manifestations, thus correlating the functions of numerous and widely separated organs.

The subject is of much more than academic importance for as an editorial writer in the *New York Medical Journal* (Feb. 26, 1916, p. 412) remarks: "Treatment based on the internal secretions, is in some instances, positively startling in its results, and bids fair to revolutionize our methods in several lines of practice; it is also eminently satisfying from a scientific viewpoint, being far removed from our old hesitating empiricism."

The endocrine glands, then, are factors of no mean import in the maintenance of that balance of activities which we call "health," and hence are worthy of more careful study and practical consideration in our clinical work. These organs and their hormones play a much more vital part than many physicians have allowed themselves to think. Variations in the activities of these organs deserve the closest attention, for too often endocrine disorder is only thought of when there is obvious disease of one or more of these glands. Since they are now definitely known to control growth and development, regulate metabolism and dominate the nervous system, more especially the sympathetic or autonomous system, their widespread activities assume a greater importance for it is quite clear that these hormones are altogether indispensable to the maintenance of the physiological harmony of the functions of the body, and, even, of life itself.

The Minor Glandular Disorders. Too often we are prone to look upon this class of disorders as rare and occasional and their diagnosis as comparatively easy because of the obviousness of such well marked diseases as cretinism, myxedema, giantism or acromegaly. This is a mistake, for functional disorders of this class are of everyday occurrence and are naturally far more important than the more

obvious organic diseases, for they are still in their earliest stages before serious disharmony has been caused; and, of course, are more responsive to suitable treatment.

Such all-essential factors in the regulation of human chemistry should be of interest to every general practitioner in his investigation of *every* condition in which disordered function is present. We should not be satisfied to know how to diagnose and treat those cases of definite endocrine disease merely, but rather should we be always on the lookout to detect and understand the importance of the insignificant and minor aberrations from the normal, for in so doing in many a case we may be able to forestall the more serious and more obvious diseases which, if left alone, may later assert themselves.

Personal interest, no less than the altruism of our profession, demands that we take first rank in these matters, for how can the true family doctor bind a household to himself more surely than by pointing out for correction some endocrine dystrophy of a child even before the fond parents have recognized the danger?

As the larger functions of the internal secretions are being appreciated, their influence both for good and for bad is seen to extend far beyond the expected limits of definite endocrine disease, for as one writer has aptly put it: "There are a number and variety of conditions which can be understood and properly treated only after full comprehension of the work of the endocrine glands." All the uncounted clinical and experimental experiences which have been directed towards the solution of the numerous problems which this ever-broadening subject has opened up, have convincingly demonstrated that the influence of the various units of the endocrine system, as well as of the body as a whole, is far more extensive and complex than even the best posted physiologists had supposed, and that many phenomena credited to nervous or sympathetic nervous influences were really the result of hormonic disharmony. In fact we know as a result of the painstaking work of Cannon, Crile, Elliott and Sergent, that as the sympathetic system is under the direct control of one or more of these hormone influences, disorders with prominent sympathetic disturbances, as shock, collapse, hysteria and other neuroses, may be traced further back than we have been in the habit of doing heretofore, and, what is of far greater practical importance, may be controlled by applying the principles which the study of this subject simultaneously has proved

possible in the domain of therapeutics. Crile's exhaustive study of the kinetic system—the adrenals, thyroid, brain and muscles—and its practical application in what he chooses to call "anoci-association," is but one of the many profitable phases of this huge subject.

Broadening the Therapeutic Horizon. Now that the interest of the aggressive section of the profession is being focused upon these glands, and much regarding their study and the importance of the many phases of the subject is appearing in current medical literature, a comparatively new branch of medicine is gradually being differentiated, and with our better knowledge of the physiology of the hormone-producing organs, there comes not merely an increased diagnostic skill, but a broadened therapeutic horizon, *for in the study of the internal secretions lies the future of the treatment of most functional disorders.* To tell the truth the extensive ramifications of this subject and the increasing prominence of the endocrine features in so many minor as well as important disorders, are awakening an interest in the new specialty. As Sajous says, this branch of medicine "claims the right to exist as a specialty, for its field is greater in scope than some which have earned well merited recognition." (Hemadenology: A New Specialty, *N. Y. Med. Jour.*, Feb. 20, 1915, p. 365.) Sajous then continues: "Its influence on the improvement of the race through the light it will shed upon the pathology of the unfit, mental and physical, cannot but prove a blessing. If to this we add the many disorders it will serve to elucidate through collective effort on the part of the host of investigators it is bound to enlist . . . the day may come when the inauguration of hemadenology may be considered as having marked a new epoch in medicine."

All who have studied this subject admit that it has a fascination that cannot be measured. The profitable applications that have been made in clinical practice by the employment of organotherapy, or "hormone therapy," explain in a good measure the favor with which this subject is being received by the medical world.

As we occupy ourselves in searching for the earliest signs of endocrine disorder, automatically we gain a better insight into the intricacies of the functions of the body and are not merely able to forestall the later and more serious organic disease, but so often we run across associated manifestations of the most diversified kinds, from nocturnal enuresis to chilblains or from neurasthenia to a stiff neck, which

may be modified directly by suitable organotherapeutic measures which we may be directing toward an associated but entirely different condition.

What Some Authorities Have Said. None can deny that a knowledge of these associated subjects—endocrinology and organotherapy—has put an entirely new aspect on the outcome of many intractable disorders. The increasing appreciation of the rôle of the endocrine glands has, as Leonard Williams has said, "lightened our darkness and shown us miracles." What other word than "miracle" can be applied to the startling effects of thyroid feeding upon the pitiful conditions of cretinism. How many of the "darknesses" of practical medicine are being illuminated by what science has taught us regarding the hormones in physiology and therapeutics, will be more evident as the reader finds opportunity to apply this knowledge in his daily routine.

In the words of an editorial writer in *American Medicine:* "Many a chronic and intractable disorder is due to an overlooked defect in the production of the hormones of the internal secretory glands. Increasingly greater stress is being laid upon the importance of these chemical messengers, and there is now little doubt that in health as well as in disease they regulate and correlate the metabolic activities of the body." Again the importance of this is emphasized in a recent review in the *Lancet* from which we quote: "As our knowledge has progressed, the influence of the ductless glandular system has proved to be far wider and more penetrating than any of the earlier investigators suspected. It controls growth and metabolism and in short determines largely the nature of that factor which the older physicians spoke of as 'constitution.'"

The internal secretions have revolutionized physiology and with it clinical medicine, just as organotherapy has revolutionized certain phases of treatment; hence the general practitioner, above all others, stands to benefit by this added fund of knowledge. As we become better acquainted with the endocrine disorders it will be noticed that intimations of their presence are staring at us in every turn in our daily routine; and we shall find many an occasion to congratulate ourselves that we have taken time to investigate this fascinating and interesting subject.

With the vital importance of the endocrine glands firmly in our minds, we may properly consider some of the information to be found in current books and medical literature regarding diagnostics of everyday clinical endocrinology.

SECTION IV. CHAPTER 2

THE MINOR THYROID DISORDERS

A full appreciation of the clinical importance of the disorders of the thyroid gland presupposes a knowledge of the essential rôle that it plays in the regulation of the functions of the body. Truly it is a most wonderful organ, and it has been called very aptly "the keystone of the endocrine arch," because it is concerned directly or indirectly in the work of practically every one of the series of ductless glands.

The Director of Metabolism. As such it is the most important single factor in the direction of the intricate workings of metabolism, for it has been well affirmed that the thyroid governs growth and development—physical and mental—controls the breaking down of certain food materials, particularly albumin, and has much to do with the regulation of the complex chemical processes by means of which the cellular wastes are disposed of. As a consequence of this many different physiological manifestations are intimately bound up with the work of the thyroid, and its functional disorders, no matter how slight, are immediately reflected in such functions as heat regulation, muscular efficiency, peristalsis, urinary excretion especially the elimination of nitrogen, menstruation and other activities of the gonads (essential sex glands), both in the male and the female, the different features of mental capacity, hematopoiesis, nutrition especially of the skin and its appendages, as well as the development of features, form and function generally.

The thyroid hormone also has to do with the powers of the body to resist disease. Sajous was among the earliest to connect its work with the production of immunity, and it has been shown to be the most important of the numerous detoxicating agencies at work in the body. This last makes the thyroid especially susceptible to the toxemias associated with the infectious diseases and the infections, in fact the chief causes of thyroid insufficiency—the minor and by far the most frequent form especially—are the infectious diseases, principally tuberculosis, syphilis and the exanthemata and, of course, typhoid, diphtheria, rheumatic fever, influenza, erysipelas and many other acute and chronic focal infections.

The Relation to the Sex Glands. The predominating influence of the thyroid upon the functions of the gonads renders it peculiarly sensitive to variations in the sexual life, especially in women; and emotional and sexual excess, as well as the toxic and functional disorders associated with pregnancy, are frequent causes of the slighter forms of thyroid insufficiency. On the other hand the sex hormones react upon the thyroid, and thyroid dysfunction is a common result of disturbed gonad function, especially of the ovaries. Incidentally this lends emphasis to one of the difficulties of endocrine diagnosis—both thyroid and ovaries react upon each other and it is sometimes difficult to know whether a given condition is causative or resultant.

The intimate relation of the thyroid to metabolism, particularly that of proteids, makes it react to that unfortunately all-too-common etiologic factor in so many disorders —overfeeding, and this is particularly true of a diet in which meat forms a generous part. Intoxications of all kinds—intestinal, alcoholic, drug and those due to ameba in the mouth or tonsils and to intestinal and other parasites —are not infrequent exciting causes of a breakdown in the thyroid function.

With the foregoing suggestions in mind, coupled with the fundamental physiological fact that the thyroid is as important a factor as any in the detoxicating and immunizing processes of the body, it will be clear that the detection of a minor functional disorder of this gland may be of much more service than merely to direct attention to the measures necessary to reinforce the work of the lagging gland. A much more important thing will have been accomplished if, in addition to this, the underlying causative element is laid bare and steps taken to eradicate it or to nullify its influence. Very, very often the proper adjuvant treatment of thyroid inadequacy—the treatment of its cause as well as its results—is made possible by applying our increased knowledge in the right way. Hence we would naturally supplement thyroid medication with emetine where alveolar or tonsillar amebiasis is present whether the infection has made itself prominent or not. Bacterial vaccines would be administered where there is a definite underlying bacterial origin, autogenous vaccines where cultures may be made easily, or, better still, mixed stock vaccines, especially where it is difficult to locate the nidus of infection and secure a culture. Again systemic alkalinization or remineralization, as the French usually call it, (see Sec. V, Chap 25) is very

much in order where acidosis and toxemia are prominent; in fact in almost every case of chronic benign thyroid insufficiency, generous and judiciously timed doses of the alkalies, preferably in proportions similar to those found in the blood, will make the response to thyroid therapy much more satisfactory. Where intestinal concretions are palpable and stasis is obvious, eliminating and lubricating remedies facilitate the best results by removing the wastes which do not merely aggravate the manifestations of thyroid disorder, but hinder every function of the body.

For these reasons, then, I rarely employ thyroid medication without some associated treatment, and am confident that many a failure in this line of therapeutic effort is due to the omission of the necessary adjunct measures; for many a time it will be found that a certain method of treatment is rendered much more efficient by the addition of thyroid (say ¼ or ½ a grain three times a day), while the reverse is equally true—thyroid therapy is enhanced by combining with it other suitable treatment the need for which is too often overlooked.

Before we pass from the consideration of the underlying basis of thyroid disorder a word of emphasis may be advantageously placed right here. Has it ever occurred to the reader that one of the commonest features of the heavy eater or drinker is obesity, and that this is also a common and quite constant feature of hypo-thyroidism? Why should the thyroid glands of those who are wont to abuse their bodies be so immune to the influence of the very factors which most commonly disturb their function? They are not, and an almost constant feature of such individuals is hypothyroidism manifested in not a few disorders other than the one just mentioned, of which we shall shortly learn. It is fair to add that these factors just mentioned are not the only causes of the thyroid type of obesity, for in some cases the cause cannot be established.

The Predisposing Causes of Thyroid Instability. All these exciting factors, and others quite similar to them, are clearly much more effectual disturbers of the chemical routine of the thyroid gland when the individual has an unstable thyroid mechanism to start with; and as with the major thyroid diseases, about which we shall have more to say later, heredity is the one great foundation upon which a susceptibility to thyroid dyscrasia is built. This is the great predisposing cause while the toxemias and other circumstances previously mentioned are the principal exciting causes.

Many conditions combine to favor the production of congenitally subthyroidic children, most important among which are various degrees of the same disorder in the parents and especially the mother. Transmitted tendencies toward tuberculosis, malnutrition and other congenital ills to which the flesh is all too often heir, are almost invariably associated with thyroid instability. Nor must we forget among causes of these tendencies, inherited syphilis—a most potent cause of every kind of functional and organic disease of the glands of internal secretion. By thyroid instability is meant, not necessarily definite thyroid disease of varying degree, but an inherent cellular weakness of the gland which permits it to succumb to the first serious stress that may be put upon it.

Usually this extra strain may be the result of some of the common infectious diseases of childhood (incidentally children with this unstable condition are just the ones who "catch everything") or it may not appear until puberty, at which period many a thyroid insufficiency of more or less permanency first makes itself manifest either by structural changes, as in goitre, or by the disturbances which result from hypothyroidism.

Early Causes of Thyroid Disorder. Other factors which favor the hereditary subthyroidism in children are toxemias during pregnancy and labor prior to their birth. I have frequently found a connecting thread between such conditions and the complex endocrine disorders which I so often see, and it would be interesting to see a report of the thyroid findings in a goodly number of individuals whose advent into the world was the occasion of eclampsia, some figures which I do not believe have yet crept into medical literature. Important among the other predisposing hereditary causes of thyroid instability are unduly frequent childbearing, prolonged lactation and like physical strains upon the system of the mother during pregnancy. Acute infectious diseases of the mother may cause this tendency in her offspring; though it should be said with emphasis that these conditions just mentioned do not necessarily spell thyroid inadequacy in the child and, of course, a constitution may be acquired after birth in spite of a poor heredity.

Perhaps additional emphasis should be given to the importance of syphilis as a predisposing as well as an exciting factor in this class of cases. We are taught to consider syphilis as a prospective cause of every obscure and difficult condition and to presume its presence until it is definitely

ruled out. This is the correct though not the usual way to look at the subject. The advent of the Wassermann test and its standardization and control by other procedures has made it possible to know with definiteness whether the syphilitic factor is present or not, and every insidious case of this character should have the benefit of the Wasserman test, at least of the blood, and not infrequently of the spinal fluid also.

Syphilis is the most insidious of all diseases and is most protean in its manifestations, and Dr. L. F. Barker, of Johns Hopkins, was right when he once told the New York Academy of Medicine that "the more my experience grows, the more I am inclined to take as a diagnostic aphorism, 'When in doubt have a Wassermann test made; when not in doubt still have a Wassermann test made.'" And in no class of disorders, is this more truly applicable than in the obscure and insidious, as in the obvious and organic, diseases of the glands of internal secretion.

Having attempted to direct attention to the numerous contributory causes of thyroid dyscrasias, as well as to the factors which are likely to precipitate slight or well marked thyroid insufficiency, we can now more intelligently proceed to consider the clinical results of this condition, and to a study of how to detect the usual and unusual symptoms of this common disorder.

From what has been said regarding the exciting and predisposing causes of thyroid disorder, it will be clear that the history, both personal and family, is particularly important as in it we may find a strong hint as to the prospective presence of the condition for which we are looking, although we may not always find a basic reason of this character in our anamnesis, for thyroid disturbances have a habit of appearing without the necessary hereditary or even the presumably essential etiologic foundation.

Hypothyroidism may be found at any time during life, from infancy to old age, though it is most common in young persons. The more serious forms are likely to show themselves in infancy or youth, while the forms that are usually overlooked altogether are more usual during the thirty or more years of active reproductive life and, as has been mentioned, it is especially frequent in women.

The Frequency of Hypothyroidism. Thyroid insufficiencies are more frequent than the exanthemata. Minor hypothyroidism is among the commonest of disorders. It complicates pediatric problems more often than almost any

other single condition except, of course, disorders of infective origin. It is equally important in the etiology of many functional gynecological troubles as well as in many of the complexities of internal medicine. Neurologists are now coming to consider it as a much more vital factor in their difficult cases than has previously been supposed and it may be considered to be an insidious complicating element in many chronic diseases including that symptom-complex usually called "neurasthenia" for the lack of a better name.

Close study is always rewarded by results which usually have a very definite clinical significance. This is as true in endocrinology as elsewhere; and to the seeing eye is unfolded many an obscure condition of daily occurrence. These are obscure merely because their insidious onset hides them. They have not been looked for. The secret of success in endocrinology is thoroughness. It is the little things that count; and it is surprising how the appreciation of a seemingly insignificant circumstance enables us to correlate some other equally insignificant condition, and thus to pass the unseen barrier which has been separating us from a full understanding of a given case.

The processes of cell-exchange, nutritional and eliminative, influence all parts of the body, hence, as Hertoghe puts it: "No tissue is able to escape the results of impoverishment of the thyroid gland." These results are just as real and important from a practical standpoint as many other obscure but none the less important disorders. They are often even more important, for their very obscurity means that their discovery may be of unusual helpfulness. The fact that they have been overlooked has made a great difference to the treatment and accounts for many failures; and their discovery may put an entirely new aspect upon the prognosis, for the treatment of internal secretory disorders with well marked and organic involvement is not always as successful as that of those conditions in which only the early, functional changes are beginning.

Infiltration, the Chief Symptom of Hypothyroidism. When we recall the principal intracellular functions of the thyroid hormone, it will be easy to understand that aberrations in the production of this chemical messenger not only interfere with cellular growth, but they derange the essential chemical changes connected with the incessant regeneration of the cells themselves. Their waste products are retained and the effete material is not burned up—facts which are proved in several different ways. The chief

result of this special form of suboxidation is the establishment of a condition of *cellular infiltration* which varies both in degree and in the number and location of the organs attacked. That it is often generalized cannot be denied, but that it is more manifest in some tissues is also true, as we shall see when the results of the more serious forms of thyroid disease are considered.

While the loss of the normal thyroid stimuli may account for many disorders, more clinical symptoms result from this infiltration than from any other single result of thyroid derangement. As we enumerate the symptoms of thyroid disorder this one factor—infiltration—stands out above all the others, and when its importance and extent, as well as the fundamental philosophy of its presence, is thoroughly understood, it will explain many a symptom which previously had not been supposed to have the least to do with this gland. The credit for the discovery and announcement of this phenomenon undoubtedly belongs to my good friend Dr. Eugène Hertoghe, of Antwerp; and to him is due the homage of the medical profession for his remarkable contributions on this subject. The importance of the whole subject may be impressed by a quotation from one of his more recent papers ("Thyroid Insufficiency," *Practitioner*, Jan., 1915, p. 27). "It is obvious that myxedematous dwarfism and infantile cretinism cannot escape detection by a physician of even moderate attainments . . . but the slighter forms of thyroid inadequacy are almost invariably missed; yet, owing to their extreme prevalence, the recognition of these is extremely important"—although more than twenty years have passed since the symptomatology of "chronic benign thyroid insufficiency" or *"myxédème fruste"* was first described.

This is just as true of the other functional endocrine disorders, and the fact that they are so very often overlooked, and information as to how to detect them is not easy to obtain, is, it is to be hoped, a sufficiently good reason for the emphasis which is being laid on the subject here.

Numerous Clinical Findings. So many organs and systems may be affected by disturbed thyroid secretion that it is necessary to consider separately the principal changes in the different tissues. It should be remarked, however, that not all of the conditions shortly to be enumerated will be found together in a given case, not even in the serious form of hypothyroidism. The detection of several of them is sufficient ground for the application of suitable thyroid

therapy. This is not empirical thyroid medication, for further proof of its scientific basis is forthcoming when the response is favorable, and Hertoghe's statement must be taken as axiomatic that "those who derive benefit from thyroid medication invariably will be found to show symptoms of thyroid inadequacy;" and if thyroid may have been indiscriminately administered—a not infrequent happening —and the results are favorable, this may be taken as a therapeutic-diagnostic test.*

Inadequate or suppressed thyroid function causes morbid syndromes in direct ratio to the loss of the thyroid hormone to the body; and this may affect almost every tissue and function. Perhaps the most common and constant changes resulting from hypothyroidism are seen in the skin and its appendages. It is infiltrated with waste products, puffy and insufficiently nourished so that it becomes dry, rough and desquamating. Sensible perspiration is reduced and in advanced cases not even exertion in summer heat will awaken the dormant sweat glands. Usually the more marked edema is only present in myxedema which will be considered later. Many dermatoses may be found. In children eczema is most common; at puberty, especially in girls, acne and in adults herpes, psoriasis, urticaria and dermal malnutrition and susceptibility to slight cutaneous infections with varying symptoms. According to Leopold Lévi, subthyroidism provides a favorable soil for recurrent erysipelas and he has found that this condition has yielded readily to thyroid.

As a result of the infiltration the hair is sparse, thin and ill nourished, falls out easily and characteristic of certain stages of this condition is the *"signe du sourcil"*—a commencing of absolute loss of the outer third of the eyebrows. For the same fundamental reason the nails are often striated and brittle, later cracking very easily. The teeth are bad, caries being a common result of hypothyroidism, and a routine finding in children with thyroid defects. In fact the child with bad teeth should be studied from this particular viewpoint, and very frequently other prominent results of the underlying hypothyroidism are discovered; and the obvious treatment will be most helpful besides local dental care.

Deficient Oxidation, the Rule. The metabolism as estimated by the calorimetric Basal Metabolism Test is de-

* Elsewhere a method of testing thyroid function is outlined. It is really a routine, uniform application of the principle just mentioned.

creased in proportion to the thyroid deficiency. The "B. M. R." often is 15, 20 or even 30% below the normal. The generally deficient cell oxidation commonly results in the temperature being below normal, and occasionally it is lower in the late afternoon at which time there may be fits of shivering, at times simulating malaria very much. There is a general chilliness and the extremities are cold. These individuals feel the cold very much and require undue amounts of clothing or bed coverings. They are continually complaining about the cold, take all sorts of precautions to guard against it and slight draughts cause rheumatoid or neuralgic pains. "Dead fingers" are often due to this cause and cyanosis and even chilblains are connected by many authorities with hypothyroidism. Raynaud's symmetrical gangrene and other forms of vasomotor spasm with skin manifestations are also credited to the same fundamental cause; and time and again have disappeared when suitable needed treatment is instituted.

Fatigue, especially in the morning, is usual. Subjects of this disorder were "born tired" and require much sleep. The cellular apathy causes them to sleep very heavily, often in the day, especially after eating. There is a feeling of depression and well-marked cases are apathetic, disinterested and "lazy."

The infiltration and generally devitalized condition naturally favors obesity. The muscles, joints and ligaments are all similarly influenced, producing such common symptoms as "rheumatism," stiff neck, aching in the limbs and back often especially marked between the scapulae. The joints may be stiff and occasional swelling may suggest arthritis and even ankylosis. Cracking noises in the joints are not unusual and Hertoghe speaks of it being very common in the knees. The involuntary muscles are also affected, the intestinal and abdominal walls are weak and ptosis is the rule. Stasis, constipation and the accompanying toxemia complete a vicious circle.

Constipation and Stasis. Many of the symptoms so widely emphasized by Sir Arbuthnot Lane were connected and described by Hertoghe 15 years before and definitely credited to "benign chronic subthyroidism." (See E. Hertoghe, *Bull. Acad. Med. de Belg.* March, 1899, p. 231.) For many years he has successfully treated such cases on this basis, and while there may be an advantage in the present vogue of intestinal lubrication and, rarely, even in the operative measures recommended, the elucidation of the

fundamental cause and its removal is a much more satisfying, as well as rational, procedure. Obstipation of the most aggravating type is not uncommon. The stools are hard because of the decreased alimentary secretion. The appetite may be progressively poor and certain foods, especially meat, are intensely disliked. The appearance is toxic and often prematurely senile and in advanced cases a brownish pigmentation of the skin has been remarked by some writers.

A sensation of heaviness over the epigastrium is not unusual and biliary colic has been caused by thyroid infiltration and nothing else; and nutrition is below par, though the weight may be normal or, more often, increased. There is a reduction in weight when our therapeutic efforts begin to relieve the infiltrated cells throughout the body of their accumulated wastes. Hertoghe uses the term "thyroid inanition" which refers to a condition of cell starvation, inactivity and asthenia without obvious changes in contour or weight. Vomiting, in some cases, may be due to this same fundamental cause, especially when associated with pregnancy.

Cardio-Circulatory Asthenia. The infiltration does not miss the cardiac muscle and in consequence the heart action is weak and the pulse usually slower than normal. Circulation is especially poor, accounting for some of the manifestations (associated with the infiltration) just connected with hypothermia. Respiratory oppression and varying degrees of dyspnea are frequent. Occasionally this is intermittent and mistaken for asthma, thus explaining the occasional unexpected cures in "asthma" following thyroid therapy. According to Hertoghe "the physiologic stimulant of the heart is supplied by the thyroid. It is, in a certain sense, the necessary tonic, the normal digitalis, by which cardiac activity is promoted and maintained. . . . I do not hesitate to exhibit thyroid extract in cases of weak contractility and tendency to syncope, and I may say that the treatment has never failed me." (See article mentioned above.)

Bladder Symptoms. The desquamation so marked on the epidermis, as well as the infiltration and loss of function due to, it, are also present in the bladder which, by the way, seems to be peculiarly supersensitive in hypothyroidism. An excess of squamous cells is common among the urinary findings, and the incessant denudation results in an undue sensitiveness to contact with the urine, causing frequent urina-

tion and enuresis, especially in children who, it will be remembered, are very heavy sleepers (with consequent decreased control over the ejaculator urinae reflex) as a result of which bed wetting is not unusual. The other urinary findings show the reduced oxidation very plainly. This is especially noticeable in the low urea output. In such cases there is often a tendency to acidosis and an estimation of the ammonia will show that generally it is unduly increased, due to the imperfect metabolism in the liver of the "urea precursors." It almost seems that there is a distinct connection between the thyroid and the liver, for in the more marked cases of hypothyroidism, not only are the chemical functions of the liver disturbed, but it becomes infiltrated, passively congested and tender on pressure. The same is true of the gall bladder and the desquamation there favors the production of gall stones or jaundice with their usual symptoms.

Mental Slowness. The mental disturbances are many and varied. Slowness characterizes every form of mental action. The memory becomes gradually poor, there is difficulty in following a line of thought or reasoning. Apathy, somnolence and melancholia and in the more marked cases organic brain disorders with varying forms of mental deficiency may be present. Headache is a usual and early symptom, especially when it occurs early in the day. It is so constant in some cases that they have accustomed themselves to it, and "have it all the time." Neuralgia and migraine have been definitely traced to the thyroid and the conclusions verified by the therapeutic test. Two insidious subjective symptoms may be present which are rarely thought of in connection with this disorder. These are giddiness and noises in the ear. The generalized infiltration is again responsible, and the same thing also may cause hoarseness, a change in the timbre of the voice, and even aphonia.

Influence on the Ovaries. The effects of thyroid dyscrasia on the gonads are well marked and among the most constant findings, especially in women. Early thyroid disorder spells late reproductive activity. Often the menses are delayed for years, or after having started may be suppressed for a varying period. Amenorrhea is sometimes noticed, especially in young girls; but in women, especially towards the close of reproductive activity, when the characteristic infiltration is present, the reverse is the rule. Menorrhagia, severe and persistent, is a common result. It is believed by

some that the thyroid has something to do with the development of the uterus, and that when hypothyroidism is fairly well marked the posterior uterine wall is not properly developed, sometimes causing a marked retroflexion which may be a part of the cause of the menorrhagia. The menses are prolonged, may recommence after they are apparently over, the frequency of the periods is increased and the loss of strength and activity is especially noticeable. "The higher the degree of thyroid inadequacy, the greater the menstrual losses." (Hertoghe.)

Many a case of severe dysmenorrhea has an important thyroid element in its causation, and this factor may outweigh all the other associated conditions. These cases nearly always show one or more of the other symptoms of thyroid inadequacy, and the success of thyroid or thyro-ovarian therapy (E. Hertoghe, *Practitioner*, Jan., 1915), will be the best proof of the correctness of our surmises.

The "Classic Picture" of Hypothyroidism. I have enumerated many symptoms referable to thyroid insufficiency, so many, in fact, that a catalogue of the possible symptoms of this disorder used to render the cataloguer open to ridicule! The fact remains that they may all occur as a result of this disorder though we may not find more than three or four of these signs in one case. However, it is by no means uncommon to find an individual showing what might be called "a classic picture" of hypothyroidism—severe headaches, neuralgia, "rheumatism," constipation, ptosis, skin disorders, hypothermia, chilliness or distinct chills, slight dyspnea perhaps better referred to as a sense of undue oppression on the slightest effort, asthenia, mental changes of a minor character—as loss of memory, inability to concentrate—menstrual disturbances, etc., etc.

Such cases, heretofore an unmitigated nuisance, both to their relatives and their physicians—for too often they have perambulated from one physician's office to another—may now be considered as of unusual profit, for their treatment by attention to the necessary hygienic measures plus thyroid therapy very often means results, the like of which cannot be obtained in any other manner. Such patients are amazed at their progress, their friends see changes in their features and their "view of life," that make for success in practice.

Let us not allow the slightest phase of minor thyroid disorder to pass us again; and let us always remember that if our diagnosis is wrong the treatment will show it!

SECTION IV. CHAPTER 3

THE MORE SERIOUS ORGANIC THYROID DISEASES

Like most organs of the body, the thyroid gland may be the subject of both hypertrophic and degenerative diseases. These exert a well-marked influence upon the physiological activities of the organism, not merely due to the effects of the disease *per se*, but more particularly because of the widespread but subtle effects of the resulting dyshormonism.

Thyroid Tumors—Goitre. The thyroid gland is commonly the seat of changes which result in the production of tumors, and while the organic disorders such as carcinoma and sarcoma are somewhat rarely found in this gland, it is considerably more frequently modified by a tumor growth known as an adenoma, which may or may not become malignant. It should be understood that these tumors may be present with no decided change in the internal secretory capacity of the gland, while on the other hand either a reduced or an increased functional activity may accompany the development of the new growth. This change in endocrine capacity may be determined by my Thyroid Function Test. (See Chapter 4 of this Section.)

Quite the most common tumors of the thyroid gland are the well-known goitres. Doubtless much of the mist that has surrounded these growths in the past has resulted from our inability to distinguish between the different kinds of goitre. The number of investigators of this subject has been large, and the amount of the work done, stupendous; but it is not fitting here to attempt, more than briefly, to mention a few facts recently developed and to tabulate the symptoms, characterizing the several kinds of goitre.

First, let us remember that goitres are of two kinds, simple adenoma, furnishing no characteristic symptoms—mere hypertrophy of the gland. In this case the enlargement seems not to interfere with the normal functioning of the gland; however, after existing thus for a number of years, without known cause and with or without increased hypertrophy it seems to furnish an increasing amount of the normal internal secretion, of which thyroxin is the active principle, attended with symptoms of hyperthyroidism. If not interfered with, this hyperthyroid activity may

take on serious proportions, and tends to grow worse, finally becoming fatal. In this stage the symptomatology does not differ from that of exophthalmic goitre, save in a few particulars. Since this kind of hyperthyroidism, as is already stated, is superadded to a simple hypertrophy of the thyroid gland which has existed for a number of years (from five to twenty), these more serious symptoms are not found until middle life or afterward. This may account for the additional fact that here strain upon the heart, caused by hyperthyroidism, becomes more and more serious causing first hypertrophy and dilatation and finally disintegration of the heart muscles. Sometimes these simple adenomas remain throughout life without developing dangerous symptoms.

Differential Diagnosis of Hyperthyroidism

ADENOMA—THYROTOXIC	EXOPHTHALMIC GOITRE
Non-hyperplastic—save in rare exceptions.	True Hyperplasia — uniformly found.
Metabolism — B. M. R. — Increased, direct result of Hyperthyroidism. Average time after beginning of tumor until the onset of symptoms—14 years.	Metabolism — B. M. R. — Increased, direct result of Hyperthyroidism. Average time after beginning of tumor until the onset of symptoms—11 months.
Exophthalmos almost never found.	Exophthalmos occurs in 87% of cases that have existed two years — (50% in cases less than 3 months duration.)
Systolic B. P. averages higher, also diastolic.	Tendency to hypertension not usually found.
Seldom appears before middle age.	Average incidence 5 or 10 years or more, before middle age.
Beginning gradual. Often unable to tell exact time when symptoms began.	Onset rather abrupt — date of commencement often can be given.
Broken compensation and myocardial disintegration common in later stages—perhaps because incidence is later in life.	Compensation in heart action common.

Differential Diagnostic Points. In the other form of goitre, known as exophthalmic goitre, the tumor undergoes hyperplasia, or the growth of new cell elements within the tumor. Unlike the adenoma this hyperplastic enlargement is attended almost from the first by symptoms of hyperthyroidism and, as in the more dangerous forms of adenoma, these symptoms grow worse and worse with no tendency

toward a spontaneous cure. The chief differences between the hyperthyroidism of adenoma and that of exophthalmic goitre are that (1) these untoward symptoms develop soon after the beginning of the enlargement of the thyroid and (2) since the subjects are usually younger than those in whom the adenoma becomes dangerous in middle life, the effect upon the muscles of the heart is not so serious, doubtless because the subjects, being younger, can better endure the overwork of the heart.

Simple Goitre. The so-called "simple goitre" may be of three distinct types: (a) Parenchymatous (increased proliferation of the thyroid structure and follicles) in which case the gland is moderately firm to the touch and regular in form; (b) colloid (increased production of the material in the follicles) with a comparatively large and soft tumor; and (c) cystic (a modification similar to the colloid form in which the follicular contents are fluid) in which there is a distinct fluctuation present.

With these several forms of simple goitre there are often no important general symptoms, although one must expect to find local disturbances depending upon the degree of pressure that may be exerted by the enlarged gland. It can be readily understood that the intrathyroid changes may diminish the secretory powers of the glandular tissue, whilst the hypertrophy causes a considerable increase in the size of the gland. This explains the presence of hypothyroidism in goitre and also the occasional value of thyroid therapy in goitre, for as Falta says: "For the most part there is sufficient parenchyma capable of functionating." When this comparatively healthy portion of the gland is not enough to supply the necessary amount of hormones, the homo-stimulant action of the thyroid which may be administered, suffices to increase the functional activity of the healthy remainders and thus augment the deficiency with resulting clinical benefit.

Thyrotoxicosis and Adenomata. With the simple form of goitre there are often no important symptoms, and, as suggested, the goitre may continue for many months or years without manifesting any unusual irritability until life ends from some other cause; but too often in middle life, as already suggested, without any known cause and without any apparent change of internal structure of the tumor, the apparently normal thyroxin may be furnished in increased quantities until the system is thoroughly poisoned, the condition being known as thyrotoxicosis. Or, again, the sound

secretory portions of the gland may hypertrophy and a condition of hypersecretion supervene—in which event the clinical diagnosis is not usually made by the local examination, but rather by the study of the manifestations of dyshormonism which accompany the goitre, and which will be referred to shortly.

The well-defined and localized goitres, or adenomata, commonly have a distinctly nodular feeling. Where there is an accompanying syndrome which includes anemia and cachexia, suspicions of malignancy are warranted. The confirmation of such suspicions is usually made after an operation, although occasionally the presence of metastatic growths is convincing though belated evidence of the malignant character of the tumor.

Thyroiditis. The thyroid gland may be the subject of an acute infectious process of varying severity. This has been seen to follow an infective process elsewhere in the body, particularly in the tonsils, as well as a number of the acute infectious diseases. Not infrequently it occurs in the primary stage of syphilis. From a diagnostic standpoint the most important findings in acute thyroiditis include the rapid onset and well-defined enlargement of the gland with extreme local tenderness, exquisite pain extending up and out of the throat, ears and neck, fever, the results of increased thyroid function—especially cardiac, and, in advanced cases, pus formation with fluctuation.

Sclerotic changes may follow an acute inflammatory process and are not uncommonly also seen in tuberculosis, syphilis and alcoholism. The direct result of this condition is likely to be a varying degree of hypothyroidism (discussed in the previous chapter) which even may become a well-defined myxedema.

Myxedema. The organic changes in the thyroid just mentioned are less frequent than these functional-organic changes which differ from the minor thyroid disorders already outlined, only in degree. The well-defined and chronic secretory disturbances of the thyroid gland are practically always accompanied by structural changes, insufficiency being associated with sclerosis or atrophy (though as we have seen, goitre is commonly accompanied by hypothyroidism) and increased activity with hypertrophy and increased vascular engorgement.

The first of these is myxedema or organic hypothyroidism. We have already seen that this may be of very slight degree with a large series of inconspicuous symptoms. It

may be more marked—the *"myxedeme fruste" of Hertoghe* —or, again, it may be so well established that the thyroid aplasia results in a typical myxedema, the symptomatology of which we now may discuss briefly. Incidentally the disorder known as cretinism is really an early myxedema or athyroidia, and, save for the well-defined development disturbances due to the earlier lack of the thyroid hormones, the symptoms are practically the same.

Naturally, one would expect to find a similarity between the manifestations of myxedema and the minor form of hypothyroidism, and this is the case, the difference being chiefly in degree. The changes in the skin are most obvious and it is due to their prominence that the disease received its name. They are dependent upon the condition of infiltration or edema (this is not really edema, for the infiltrated products are mucoid rather than fluid and there is no pitting on pressure), which causes well-marked trophic changes in the skin itself, as well as in the dermal appendages. The color of the skin is a buff-pink, sometimes almost grayish. It is said by some to look like alabaster. It is puffy, dry, desquamates easily, and the sweat glands are inactive. The skin is often unusually susceptible to local infections. The hair is dry and brittle and falls out in large quantities. The nails crack easily and are dry and poorly nourished. The teeth are almost invariably in very bad order.

The vital processes as a whole are reduced to a minimum. The temperature is from one to several degrees below normal, metabolism is reduced and with it the elimination of wastes by all channels. Toxemia is, therefore, the rule and this favors a condition of invincible constipation which is also usually present. Despite this toxemia the heart action is usually reduced with a slow pulse and a tension often much below normal, due to the associated adrenal insufficiency which will be considered in another chapter. As a further result of this there is a well-marked anemia and especially a hemoglobinemia.

The retrograde changes in the mental powers are very marked, in fact the whole of the nervous system is extremely inactive. The reaction of the body to external stimuli is very poor. Mentality may vary from dullness to complete amentia, and in early cases, loss of memory and inability to concentrate and the general disinclination to use the mental powers are the rule. The term "logey" is often applied to these cases.

Impotence is the rule in men, and in women either amenorrhea or menorrhagia. (In the first instance the gonads lack the stimuli from the thyroid which are undoubtedly a factor in establishing and maintaining the molimena, while in the latter the infiltration of the myometrium and endometrium coupled with a subtle change in the chemistry of the blood may cause an increased and prolonged menstrual flow.) Atrophy of the genitalia may take place, but is not so marked as in pituitary disease, of which more later.

Cretinism. In infantile myxedema or sporadic cretinism, in addition to the findings previously mentioned, there is an almost entirely retarded mentality and physical backwardness and, of course, the sexual development is practically stopped. The face has a broad, puffy, "sloppy" appearance, the "saddle nose" is frequent, and the capacity to respond by a smile, a twinkle of the eye, or motions of the facial muscles, is almost entirely lost—but this is mental, as suitable tests will show no paralysis present. The mouth hangs open, the lips are large and the teeth are delayed in their eruption, and when seen are carious and widely spaced. The bones are abnormally formed, short and stubby. The figure is deformed, the gait awkward, and sometimes walking is impossible. Coördination is poor. The abdomen is soft and prolapsed, the condition known as "pot-belly" being frequent. The cretin does not grow up and the mental and physical stigmata make a pitiable picture.

The general metabolic inactivity favors the deposit of fat and the condition of thyroid obesity is quite common in cretinism as in the minor hypothyroid insufficiencies.

A word should be added here about "endemic" cretinism as compared with the "sporadic" form just mentioned. This condition is extremely rare in the United States, but common in Switzerland and Austria. The distinction lies in the heredity: endemic cretins are descended from cretin families and are born in places where cretinism is prevalent. The clinical manifestations are, perhaps, not always so completely typical as in the sporadic form, and occasionally procreation is possible. In addition to the stigmata of cretinism already outlined, umbilical hernia is very common in the endemic form of cretinism. Deaf-mutism is very often associated with thyroid aplasia. According to Scholz nearly 30 per cent. of the endemic cretins seen by him were deaf mutes.

There is another important distinction between these two forms of cretinism—the sporadic form responds wonder-

fully to thyroid medication, while the endemic form may or may not be benefited by this method of treatment.

Hyperthyroidism*. The other principal form of thyroid dyscrasia is hyperthyroidism, and is the best known and most complex of all the functional thyroid diseases. Here the thyroid gland is unusually active with or without a marked increase in its size. This condition is most commonly called "exophthalmic goitre," though an excessive thyroid secretion may be present without the exopthalmos, and, rarely, the exophthalmos may be present without the goiter. Parenthetically, the use of a physician's name to identify this disease is confusing. Parry discovered the syndrome first (1786). Flajani described it again later. Graves explained the syndrome intelligently (1835), while von Basedow (1843) gave a better description and connected the disorder more definitely with its real cause.

A few words as to the principal causes of this complex disease may facilitate our study of its diagnosis. Three great factors must be taken into consideration: Focal infections; fright and emotional affections and the hereditary thyroid instability so well emphasized by Léopold Lévi and discussed previously. Fright and excessive emotions are not uncommonly connected with the onset of a severe degree of exophthalmic goitre and Cannon's recent researches into the relation of the emotions to adrenal excitation may be the basis of a satisfactory explanation as to how this is caused. For instance, it is quite possible that the undue stimulation of the adrenals thus brought about may so decidedly push the thyroid pendulum as to cause it to swing very much more rapidly and widely than is normally the case, while the resulting dyshormonism may prolong the effects, for the thyroid itself is just as susceptible to the thyroid hormones in the blood as are any of the other organs of the body.

Toxemia, usually of bacterial origin, is probably the most common cause of this disease, and a careful study very often will reveal some focus of infection in one part of the body or another. Most common among these sources of bacterial poisoning are the tonsils, nasal fossae and adjoining sinuses, teeth and gums (and especially around the roots of the teeth), colon (especially the angles), gall bladder and pelvic

* The first issue (Jan., 1921) of *Harrower's Monograhs on the Internal Secretions* is entitled "Hyperthyroidism: Medical Aspects." It contains a comprehensive study of the subject with bibliography. (120 pages; sewed; $1.50, postpaid. Annual subscription, $3.00.)

organs; probably in the order mentioned. Undoubtedly there is also a connection between the incidence of hyperthyroidism and the gonads, especially in women, and the frequency of this disease in women, about 10 to 1, and the common relationship of menstrual disturbances with it, and *vice versa,* are sufficient confirmation of this. That these gonad disorders are usual in individuals with that subtle disorder named *"l'instabilité thyroidine"* and that an hereditary defective thyroid substratum favors the onset of dysthyroidism, is well borne out by those who are in the habit of making a thorough anamnesis.

Aside from the two symptoms embodied in the name—exophthalmos and goitre—symptoms which we need not dilate upon here, the most obvious diagnostic finding is the serious change in the heart action. Tachycardia is practically the rule, the pulse ranging from 120 to 180 beats per minute. With this is an extreme degree of nervous irritability or sympatheticotonus, a good part of which, in the estimation of the writer, is due to the functional adrenal and circulatory changes, although there are cases in which these nervous manifestations have nothing to do with the heart. The cardiac excitability—it is often of a heaving, pounding nature—is responsible for the pulsation not merely of the goitre itself, but of various vessels throughout the body, and this persistent beating in the head, the abdomen and especially the throat and neck is a very uncomfortable symptom. The undue strain on the heart often causes dilatation and even incompetency. Myocarditis is the most common and serious result. Some writers mention the auscultation of a murmur over the goitre.

As might be expected, the metabolism is decidedly plus. (See especially the references to various laboratory tests in Chapter 12 of this section.) All the cells are working overtime as a result of the excessive thyroid stimuli and this is doubtless responsible for the hyperthermia which is quite common in the well-marked cases of this disease. It also accounts for the loss of weight (despite the not infrequently increased appetite and intake of food), the increased perspiration and, probably, for the sharpened mental activities. In this connection one of the difficult features of hyperthyroidism is the control of the mental status with its disturbances of concentration in work and its effects upon insomnia. It has been remarked by several writers, and especially by Leonard Williams, of London, that among the earliest signs of excessive thyroid action is a tendency to

genius—such individuals have great ideas, lean to literature or the arts, take up fads, and are far from dull in their studies or their work.

With the decided effects of myxedema upon the skin in mind, one would expect some opposite changes in the skin in this opposite condition, and this is the case. The skin is usually thin and delicate, is moist and well-nourished by a very good blood supply. The skin reddens under the slightest local or emotional influence and the sweat glands become active on the least provocation until the hyperidrosis is more than a nuisance. Occasionally this is one of the earliest symptoms and night sweats of thyroid origin have led the diagnostic scent away from the right trail.

The toxemia, sympathetic irritability and cardio-vascular excitability together form a combination which may produce many and varied symptoms only a few of which need be enumerated, i. e., tremor, twitchings of the eyelids and face, restlessness, insomnia and often a decided neurasthenia. Myasthenia with an aggravating fatigue and much discomfort on exertion are usual and to be expected in a disease in which the hormonic balance is so thoroughly disorganized.

The late symptoms of exophthalmic goitre include serious heart changes both in the sounds and the rhythm. Heart failure is a common cause of death from this disease. Dyspnea and severe diarrhea are also ominous signs when found accompanying other signs of hyperthyroidism.

SECTION IV. CHAPTER 4

A METHOD OF TESTING THYROID FUNCTION

Many times the reaction of an individual to organotherapy serves as a fairly good index to the condition of the endocrine glands which correspond to the gland from which the extract was made. That is to say, individuals with a sensitiveness in a given gland are likely to react more quickly to organotherapy than those in whom there is an apathy. This is more particularly true of the thyroid, and many hundreds of physicians have given thyroid extract to patients and in a short time had to discontinue it because it made them nervous and irritable, unduly stimulated the heart and evidently was not accomplishing what was desired.

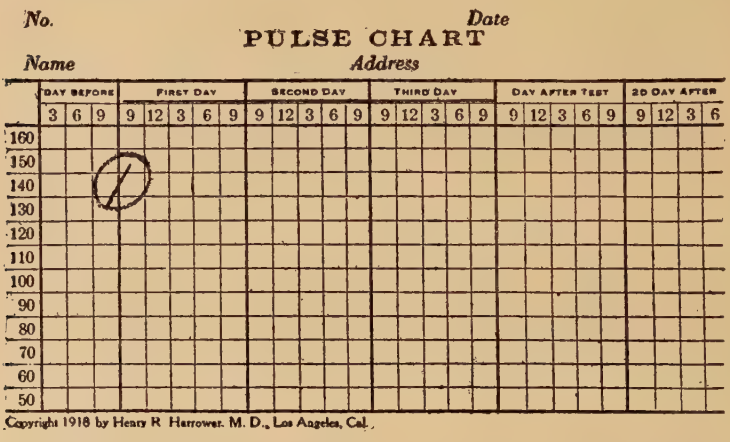
Routine Thyroid Feeding. Based upon a number of clinical experiences of this character, I have devised a very simple, but none the less useful, method of testing thyroid function, which was announced originally in the New York *Medical Record,* August 3rd, 1918. The test consists of giving definite and increasing doses of thyroid extract, with a suitable inert excipient, in a uniform and routine manner, while a careful study is made of the pulse, and any other symptoms which may occur. The information obtainable in this manner is of much service, for it amounts virtually to a differential diagnostic measure in the study of goitre.

It will be recalled that from the secretory standpoint there are two distinct varieties of goitre: (1) the simple enlargement of the gland, which appears to be an effort on the part of the organism either to supply an increased demand for its particular product which may be deficient, or to produce a greater supply than usual because of an increased demand for it; and (2) the hypertrophy which is due to some extra-glandular cause, such as toxemia or any form of irritation. The former, or simple goitres, are a useful attempt on the part of the body to render the best service possible under the circumstances and usually are benefited by a course of treatment which includes the administration of thyroid, iodin, etc., which thus tends to supply the need, in part at least, and render the friendly enlargement of the gland unnecessary. Parenthetically, in these cases of simple goitre, the administration of *Iodized Thyroid Co.* (*Harrower*), which contains a suitable dose of thyroid extract, iodide of iron and nuclein, serves very satisfactorily to supply the right kind of stimuli in such circumstances.

In the other class of cases, however, the conditions are decidedly different, for the thyroid gland is being overworked, and driven faster than normal. This is usually brought about (1) by the toxins absorbed from foci of infection, (2) from emotional disturbance or (3) from deranged functions of some of the other endocrine glands. In such cases, the thyroid gland is more sensitive and hence more unruly; and just as the hypertrophy differs very materially in origin, so it differs in its responsiveness to thyroid treatment. In fact, what would be most beneficial in simple goitre would be most detrimental in the goitre due to hyperthyroidism, and the administration of my Thyroid Function Test enables one to differentiate the early functional stages of thyroid sensitiveness, i. e., between latent

hypo- and hyperthyroidism, and thus accomplish something worth while in the treatment.

The materials for the thyroid function test consist of four doses each of a half, one and two grains of thyroid in graduated capsules together with a chart similar to the one illustrated (Fig. 1), to which is attached printed instructions as follows:


No. Date

PULSE CHART

Name Address

	DAY BEFORE			FIRST DAY					SECOND DAY					THIRD DAY					DAY AFTER TEST					2D DAY AFTER				
	3	6	9	9	12	3	6	9	9	12	3	6	9	9	12	3	6	9	9	12	3	6	9	9	12	3	6
160																											
150																											
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70																											
60																											
50																											

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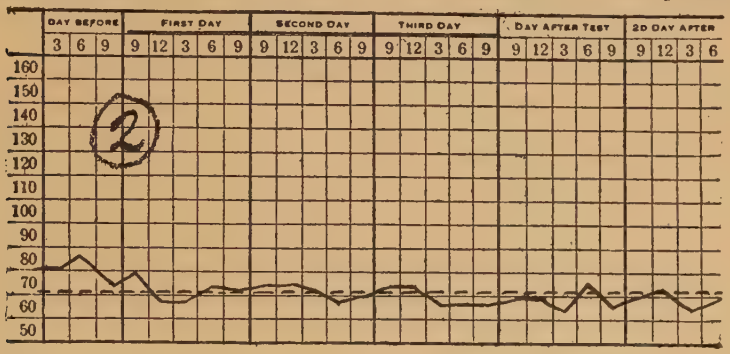
Instructions for Using the Test. Each package of Thyroid Testing Capsules contains 12 capsules of three graduated strengths and sizes. A pulse chart accompanies each, with explicit instructions as to how to fill out the record.

After the consultation, at which the first pulse-counting is done and recorded, the patient counts the pulse again at 6 and 9 o'clock; and the following morning commences to take the four *small* capsules at 8, 10, 12, and 2 o'clock with a swallow of water, recording the pulse five times a day—at 9, 12, 3, 6, and 9 o'clock. On the second day the four *medium*-sized capsules are taken at similar hours and the pulse is again recorded under as nearly identical conditions as possible, and at the same hours.

During the third day the four *large* capsules are taken at the same hours as previously and the pulse is again recorded as before. The fourth day, or the "first day after" finishing the ingestion of the capsules, the pulse is recorded as before and again during the forenoon of the fifth day ("second day after") when the chart is completed (and plotted, if convenient), the physician is consulted and the data thus secured carefully studied.

It is important to watch for symptoms such as irritability (temperamental or nervous), twitchings (of the eyelids, fingers, etc.), breathlessness and other nervous manifestations. If it should happen that on the second or third days these symptoms are present *and prominent,* the remaining capsules should not be taken; *but the chart is completed,*



while on its reverse side a brief statement is made of the symptoms, giving the time of onset and other related facts.

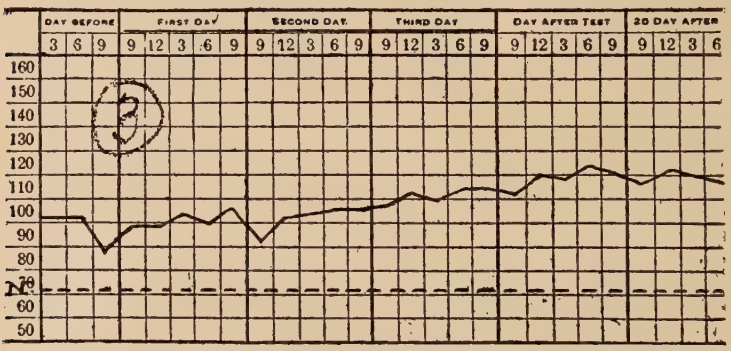
Note: Take the pulse under as nearly uniform conditions as possible, preferably before eating, after a ten-minute rest, and sitting. Mark the chart in the proper square with a dot at approximately its relative position, e. g., 72 would be just above the 70-line, 86 would be about the middle of the space between the 80- and 90-lines, etc. Be regular and persistent. The information thus obtained is worth all of your trouble!

The Clinical Reaction to the Test. The reaction of the patient to this routine administration of uniform doses of thyroid varies very materially, depending upon the factor that we are attempting to discover. In the apathetic hypothyroid cases, practically no difference in the pulse figure is found, and as in these cases cardiac action, like practically every function of the body, is lazy and slow, the pulse figures are low and remain so.

The reaction to the thyroid testing capsules in a case of functional hypothyroidism which had not yet advanced to a stage where the usual findings of myxedema are noted, is nicely illustrated on the accompanying chart (see Fig. 2). Here it will be noted that the pulse is below the normal and does not seem to be influenced whatever, even by the heavy dosage of thyroid which is given on the third day.

In the normal individual, on the other hand, the thyroid feeding is going to temporarily stimulate the thyroid func-

tion, and hence, through it, the heart rate, and it is customary, during the third day of taking the capsules, for there to be an increase in the pulse, which, however, is due to the administered thyroid extract rather than to any excess of the thyroid hormone which may be produced in the body; and since these products are destroyed quite rapidly,

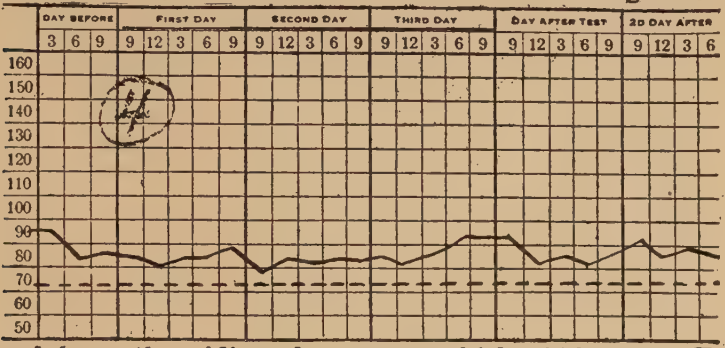


the cardio-stimulant action merely lasts during the time of the greatest dosage of thyroid *and comes down to normal again the day after.*

On the other hand, in the various stages of thyroidism, the pulse findings are characteristic: the greater the susceptibility, the wider the range. First of all, as will be noted in the accompanying chart (Fig. 3), the average pulse rate is somewhat higher than normal, and there is also more irregularity than usual. Early in the administration of the thyroid, the pulse begins to be more rapid until, during the height of the temporary gland feeding, it may reach well above any possible normal figure—100, 110 or even higher. Since this stimulus is not entirely due to the product which has been administered but to the increased activity of the supersensitive gland, following the removal of the medication, i. e., "the day after" and, "the second day after," *the pulse still remains up* because the thyroid is working overtime, as is indicated very clearly on the chart. In fact, in well defined hyperthyroidism with tachycardia this test should not be used, nor need it be, for the diagnosis should be clear without it, and in latent cases in which there is an unexpected degree of thyroid sensitiveness, it will be noted that the routine advice calls for the omission of the last four capsules—the largest dose—but the continuation of the pulse tracing, with a note to that effect upon the chart. In such cases, the variations in the pulse findings will not be so

exaggerated, merely because the test has not been completed, but the indications are equally obvious and helpful.

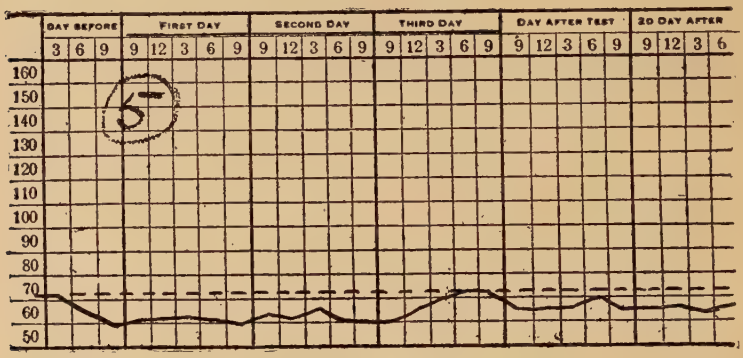
The Discovery of Latent Thyroid Conditions. This test is more useful in the discovery of thyroid apathy or a latent degree of thyroid sensitiveness than in the diagnosis of



frank hyperthyroidism, for reasons which will be clear. Two out of many hundreds of cases that have been tested in this manner showed charts which were quite unexpected and worthy of comment. The first was an individual with a highly nervous attitude, staring eyes, fine tremor, sweating palms and general sympathetic irritation. He was sent to me as a "typical case of hyperthyroidism," yet some of the findings were missing, especially the fact that the pulse was approximately normal. A thyroid function test was made and the following chart secured (Fig. 4), and later an X-ray examination of the chest showed a sub-clavicular tumor of considerable dimensions. The sympathetic irritation was due largely to the pressure of this intrathoracic tumor, and the patient did not have "typical hyperthyroidism" after all.

Another case of an opposite character had a large goitre which was about to be operated upon for cosmetic reasons. The physician about that time happened to hear of this test, tried it and later sent me the accompanying chart (Fig. 5), from which it seemed clear that the patient had a well-defined degree of thyroid inactivity, and at my suggestion various other symptoms of Hertoghe's disease—*"myxedème fruste"*—were discovered, the patient was given medication calculated to stimulate the thyroid and ovarian functions, and the goitre almost disappeared eventually, and the menstrual difficulties, which were quite prominent, were controlled simultaneously. In this particular case, the thyroid function test saved an operation by giving broader information in regard to the patient.

The Test in Chronic Disease. Still one other class of cases may benefit materially from the use of this test: I refer to the chronic toxic and nutritional disturbances such as rheumatism, neurasthenia, tuberculosis, etc., in which



elimination is very much below par and there seems to be a radical reduction in the oxidizing process. In such cases, a thyroid function test may indicate a marked degree of thyroid apathy and direct attention to the possibility of stimulating this deficiency, with decided prospects for benefit from the obviously necessary thyroid therapy. It is perfectly true that many such cases may receive benefit from the use of thyroid extract without the test, but there is a much greater satisfaction in having a definite reason for each procedure when this is possible.

My reference to tuberculosis calls for a word of explanation and caution: Many tuberculous persons have a well-defined thyro-adrenal insufficiency (see Sec. V, Chap. 2), and the thyroid function test indicates this clearly; so do the blood pressure and the uranalysis. This naturally calls for obvious associated gland support that should receive attention. On the other hand, since the thyroid gland is expected to react to stimuli of a toxic nature, a latent degree of hyperthyroidism indeed may be present and easily discoverable following this test, in which case any glandular treatment which might be in order would be the opposite from that given to the other tuberculous persons in the large class mentioned previously. In such cases, instead of using the cell-stimulating *Adreno-Spermin Co.* (*Harrower*), a preparation containing pancreas, which tends to neutralize sympathetic irritability, would be better (see Sec. V, Chap. 10).

It has been said that this thyroid function test is nothing

but the administration of thyroid extract and the usual noting of the patient's reaction, but unfortunately most of our experiences of this character have been our failures, and our clearest recollections about them were the remarks made about the uncomfortable feelings which resulted from the administration of the thyroid extract for a week or two, and caused us to stop it at once. Further, the fact that this test is ready to use, that there are printed instructions and a chart available, directs attention to and makes convenient a measure which ordinarily may not be thought of; hence I feel justified in emphasizing the importance of this procedure, not merely in the differentiation of goitre as indicated, but in the search for scientific reasons for the use of thyroid extract as a part of the treatment in a given case.

SECTION IV. CHAPTER 5

THE ADRENAL GLANDS IN HEALTH AND DISEASE

Perhaps more profitable research has centered around the adrenal glands during the past twenty years than around any of the other glands of internal secretion. At least many epoch-making discoveries of their important rôle have been made quite recently.

Unfortunately, the clinical application of this new knowledge has not been very extensive as yet; and many times the physician's sole appreciation of adrenal disease consists of a hazy recollection that Addison's disease is said to be a tuberculous involvement of the adrenal glands—and that it is incurable.

Some things about the adrenals are very well known. We are in the habit of using adrenalin almost every day and know that it exerts a decided influence upon the circulatory system, both in physiology and in therapeutics. We also know that the adrenin continuously produced by the adrenal medulla is the principal regulator of vascular tone and that it performs a number of other useful services for the body. But, somehow or another, it is the exception to find a proper clinical appreciation of the importance of the work of the adrenals and how easily their functions may be influenced slightly or seriously with corresponding minor or important effects on the body as a whole.

Fifteen years ago T. R. Elliott, of London, showed us that adrenin virtually controlled the autonomic and sympathetic nervous systems. Sergent, of Paris, had already proved this relationship in numerous experiences in his clinical work. Still more recently Cannon, of Harvard, has given us an entirely new conception of the extreme importance of adrenin to the human economy especially in so far as its variations are related to the emotions.

Some Points About Adrenal Physiology. A brief exposition of the physiology of the adrenal glands will prepare us for a better understanding of their secretory disorders. The chromaffin hormone, otherwise known as adrenin, arising from the medullary portion of the adrenals, as well as in other chromophil cell collections in different parts of the body, exerts a very remarkable and extended influence upon numerous structures which are controlled by the sympathetic. Adrenin raises the blood pressure and has much to do with its maintenance at the average level; it dilates the pupils and excites the flow of tears and saliva; it contracts the minute muscles of the hairs (erectores pilorum); undoubtedly it is concerned with the function of the sweat glands and, in fact, the blood supply of the skin and, in addition to all this, it seems to have a certain influence upon the gastric, uterine and intra-abdominal muscles in general.

Adrenin is probably the principal factor in the maintenance of the normal tone of the body, and disturbances in its production disorganize the so-called "sympathetico-tonus," causing it to be deficient or abnormally increased as the case may be. The condition known as "adrenin sensibility" is now being used as the basis for several tests for sympathetic functioning which will be referred to later.

The adrenals are particularly susceptible to what have been termed the "emergency conditions." Cannon's well checked experiments have definitely proved that the emotions, including pain, rage, fear and hunger (perhaps it will be shown later that even worry has a similar effect) influence the secretory powers of the adrenals, with an immediate response due to the hyperadrenia thus produced. This condition passes rapidly because adrenin is oxidized with unusual facility, and as soon as the glands have been sufficiently overworked and the stimulation continues with no opportunity for recuperation, a serious condition of hypoadrenia supervenes.

While comparatively very little therapeutic advantage has been taken of the results of this work, we can now see

rational explanations for a number of phenomena which quickly can be called to mind. Practically the whole of the results of Crile's investigation of "the kinetic system" and his now fairly well known method of "anoci-association" are really dependent upon the prevention by suitable measures of any undue stimulation of the adrenal glands, and hence the serious consequences of acute hypoadrenia are thereby forestalled. It will be recalled that Crile emphasized the fact that the kinetic system embraces the adrenals, thyroid, brain and muscles, which coöperate to "drive" the body. The adrenals are probably the most important of these kinetic organs and the method of pan-anesthesia named "anoci-association" consists in supplementing the usual anesthetic measures by removing such mental and nervous stimuli (by preventing fear and pain and by "blocking" certain nerves) as would tend to stimulate the adrenals and by their depletion bring on shock and collapse.

Before considering the symptomatology of the functional adrenal secretory dyscrasias, it should be recalled that not only are emotional factors already referred to capable of causing this adrenal syndrome, but that certain of the hormones produced in other organs, when present in the blood stream in unusual amounts (see further references to this in the chapter on the ovaries) may have a similar stimulating effect. We must also remember that toxemia of intestinal or bacterial origin exerts a like influence and that it has been shown that conditions associated with extremely high blood pressure cause adrenal disorder, probably by producing intra-adrenal hemorrhages. One of the best established "symptoms" of senility is of adrenal origin.

With these facts in mind we can understand that severe emotional conditions, sudden or prolonged; acute infectious diseases, with the invariable accompanying toxemia; and chronic infections, as tuberculosis or intestinal stasis (which is, after all, practically a chronic infection with mechanical involvement added) would be likely to bring about certain changes in the activities of the organism as a result of the influences due to adrenal derangement.

Hyperadrenia. Hyperadrenia is not nearly so common a symptom as hypoadrenia, although necessarily just as frequent, for the adrenal depletion of which we shall shortly speak is really a terminal condition which results from the exhaustion following excessive stimulation. The reason that hyperadrenia is not more commonly detected is probably due to the fact that adrenin is oxidized in the blood

with great rapidity, and that if large quantities of it happen to be brought forth, they are destroyed very shortly after they are produced. Confirmation of this destructive influence is noted following the use of adrenalin for therapeutic purposes, as well as in many experiments on animals which uniformly show that once this hormone gets into the blood, it is very quickly destroyed. Incidentally, this is also emphasized by the fact that adrenalin is not as effective or suitable for prolonged adrenal support as adrenal substance; for while adrenalin undoubtedly homostimulates the adrenals, it does so suddenly and actively, but the effects are ephemeral; while on the other hand, the use of the total gland favors a reëstablishment of the depleted adrenal functions, though the action is slower.

It will be proper to enumerate several clinical findings which are probably of adrenal origin, since the treatment is largely preventive rather than direct, for to realize that certain factors are unduly stimulating the adrenals, is to realize that these factors must be abated.

An unusual tendency to goose pimples, without any ordinary reason therefor, may be directly due to this condition. Probably this accounts for the not uncommon association of this phenomenon with fright. Chills, which are merely severe vaso-motor disturbances with muscular spasm, are commonly produced artificially by injections of adrenalin (especially following its use in the control of asthma), and I am by no means sure that this chief manifestation of malaria is not due to a temporary and excessive stimulation of the adrenal glands by the sudden unloosing of the toxins of the plasmodia. Further, the severe reaction following this positive phase of malaria, with its prostration, asthenia and depression, stimulates the symptom complex of hypoadrenia, as we shall shortly see.

In studying the relation of the adrenal glands to the toxemia of tuberculosis, Pottenger remarks that the continued stimulation of the adrenals and the pouring into the blood stream of minutely increased amounts of adrenin, have the effect of producing a prolongation of the condition which is originally brought about by sympathetic stimulation. It is suggested that this condition of hyperadrenia is responsible for the dry mouth frequently seen in tuberculosis, and that other symptoms of sympathetic origin, such as the sudden and seriously impaired digestion and, particularly, the rapid heart action, are really the results of excessive adrenal stimulation. Without a doubt hyperadrenia

unduly stimulates the thyroid and *vice versa*, hence the symptomatology of adrenal excess and hyperthyroidism is similar, and it is difficult to differentiate the origin of a given disorder.

It is quite possible that certain cases of purely functional hypertension, with no renal, cerebral or vascular findings demonstrable, are really due to hyperadrenia, usually of toxic origin. At least the interesting though academic researches of Zimmern and Cottenot, of Paris, seem to confirm this. They were able to reduce very high tensions by properly dosed roentgenization of the areas over the adrenals—to my mind a very serious undertaking. Parenthetically, some quite profitable studies of the treatment of functional hypertension have been based upon this fact and on the well known antagonism exerted by the pancreas upon adrenal function. This is considered more in detail in Section V, Chapter 15.

There is still another form of hyperadrenia which must be mentioned though it is very rare. I refer to the condition known as "hypernephroma," which is an excessive proliferation of the adrenals usually involving the corticular tissue more than the medulla. The chief manifestation of this is a remarkable increase in the development and growth in early life (this is much more common in young subjects) with premature sexual development. Bullock, Sequeira and others have demonstrated a relation between the presumed internal secretion of the adrenal cortex and the gonads. At all events in cases of this disease the findings are chiefly referable to the gonad functions—a child of eight or nine may be quite as large as an adult with marked overdevelopment, physical and functional, of the genitalia, and hypertrichosis. It is a difficult, practically hopeless, surgical condition.

Adrenal Insufficiency.* Since the adrenals are so extremely susceptible to so many outside influences it is likely that they would be easily "worn out" and, as a matter of fact, functional hypoadrenia is as common a condition as any endocrine manifestation. From a practical standpoint, this is an extremely important symptom-complex.

It is quite some years since Sajous began to emphasize the importance of this condition, and while his opinions were scouted and some of his ideas declared visionary it must be admitted that our present knowledge of this subject is very much in harmony with the following quotation from Sajous' monumental work: "Functional hypoadrenia

is the symptom complex of deficient activity of the adrenals due to inadequate development, exhaustion by fatigue, senile degeneration, or any other factor which, without provoking organic lesions in the organs of their nerve paths, is capable of reducing their secretory activity. Asthenia, sensitiveness to cold and cold extremities, hypotension, weak cardiac action and pulse, anorexia, anemia, slow metabolism, constipation and psychasthenia are the main symptoms of this condition."

Hypoadrenia is a complication of all the serious acute infectious fevers, since the adrenals are so intimately connected with the "driving" of the body and are so susceptible to toxemia, that the ultimate reduction of the accustomed adrenal stimuli is responsible for a slowing down of many of the sympathetic-controlled functions of the organism. Too often this sympathetic asthenia is the actual cause of death from disease of this character.

There are three forms of hypoadrenia which differ sufficiently from one another to be discussed separately:

(1) *Functional Hypoadrenia*—a temporary deficiency in the production of the chromaffin hormone is shown most frequently by a tardy response of the circulatory system to its accustomed stimuli and the development of a condition of circulatory inefficiency, the so-called "hyposphyxia" of Martinet. This is a condition of the circulatory semi-asphyxia with venous stasis, insufficient arteriolar circulation with cold extremities and occasional slight blueness (often a mottled appearance) of the skin on different parts of the body, especially the exposed parts. In such individuals the blood pressure is usually very low, 90-100 mm., although it has been shown that extreme degrees of tension may cause a functional insufficiency of the adrenals by localized hemorrhage into the glands.

Urticaria and other severe vasomotor skin symptoms are among the well marked findings in persistent hyposphyxia, while lesser degrees may cause flushings and sensations of passing distress localized in various areas of the skin. The adrenal origin of some forms of urticaria is seemingly confirmed by the occasional "miraculous" disappearance of large and most uncomfortable wheals following a single

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* The subject of hypoadrenia is so large and the literature so extensive that an entire issue (Jan. 1922) of *Harrower's Monographs on the Internal Secretions* is devoted to the study of "The Adrenals in Everyday Medicine." (120 pages; sewed; $1.50 prepaid. Annual subscription $3.00.)

hypodermic injection of from 5 to 10 minims of adrenalin solution.

Besides the circulatory syndrome the muscular and nervous manifestations are important. Asthenia is the rule and muscular tone (both striped and unstriped muscle) is poor. Exertion is impossible and "the fatigue syndrome" is prominent. The intestinal musculature is inactive and stasis, a common cause of hypoadrenia, is also a usual result of it. According to Tom Williams, mental exertion, even the simplest, often causes so much weariness and exhaustion as to be prohibitive. Mental elasticity is lost and there is both mental and physical depression with the fear that the individuals cannot now accomplish their accustomed good mental work; and the story that they "have lost their nerve." With this, one frequently notes a fearfulness of making wrong decisions and a vacillating and indecisive frame of mind. This is the most usual form of adrenal insufficiency. It is chronic both in origin and in its course. The greatest single cause is chronic toxemia either of alimentary or focal infective origin. Fortunately the control of the cause and suitable "adrenal support" (see Sec. V, Ch. 1) is followed by very encouraging results.

(2) *Progressive Hypoadrenia.*—Here we expect more than the mere functional derangement just discussed. This is really another name for the disease we have been taught was first named by Addison in 1855 which, like all organic diseases, may be seen in differing forms and stages. The main symptom is the aggravated asthenia with marked myasthenia. In well advanced cases there is a localized bronzing of the skin and mucous membranes due to the deposition of a dark pigment of undecided origin. Extreme cardio-vascular debility is the rule and the blood pressure may be as low as 30 to 50 mm. Hg. Varying gastrointestinal disturbances are usual. Happily, this disease is rare, as unfortunately its outcome is hopeless, though temporary relief has followed adrenal medication.

Lawrence connects hypofunction of the adrenal glands with weakness and apathy, marked fatigability and a tendency toward vertigo. These are merely variations in degree of the classical symptoms first reported by Addison.

(3) *Terminal Hypoadrenia.*—This is the extreme functional adrenal insufficiency which has already been briefly mentioned. It occurs in the final stages of fatal infectious diseases. For instance, the principal clinical manifestations of Asiatic cholera (the algid stage) are adrenal in origin

and, remarkably enough, have been promptly and successfully controlled by heroic doses of adrenalin, for in such cases the tolerance to the drug is apparently greatly increased and as much as an ounce of the commercial 1:1000 solution well diluted with saline solution has been given intravenously during a single day with splendid results (Naamé).

Shock, collapse, cardiac failure and distressing asthenia are terminal findings in this class of cases. Distressing meteorism is present and is presumably due to functional intestinal paresis which, by the way, can be experimentally produced by fright or toxemia and the resulting acute hypoadrenia. With these dread symptoms there is often found a noticeable reduction in the reaction of the organism to urgently needed medication, for with the adrenal activities suspended, the responsiveness of the body to stimuli of this character is practically nil.

The ominous sign of a suddenly reduced temperature is often seen and is due to the same cause. In such cases one can invariably produce Sergent's *"linge blanche surrénale,"* a dermographic sign consisting of a white line upon the skin which follows penciling the abdomen with the finger nail, and sometimes lasts for two or three minutes. This valuable clinical sign is said to be pathognomonic of acute hypoadrenia and is very easily elicited.

In cases of the character just considered, despite the severity, the therapeutic test is often both encouraging and confirmatory, for the response to hypodermic or intravenous injections of adrenalin solution and, in many cases, the early administration of this remedy by mouth, is many times nothing short of marvelous. At times I feel that this phase of adrenal medication deserves to be classed with thyroid in myxedema and with quinin in malaria. At least it is worth recommending both as a prophylactic of such likely ultimate results, and also as a last resort in their treatment.

Neurasthenia as an Adrenal Syndrome.* The minor form of functional hypoadrenia is more common than some have appreciated, and the fact that there is a psychic origin as well as the other physiologic causes already considered, allies it to the fashionable neurasthenia of today. In fact,

* The second (April 1921) issue of *Harrower's Monographs on the Internal Secretions* is entitled "Neurasthenia: An Endocrine Syndrome," and takes up all of the various aspects of the subject. (92 pages; sewed; $1.25 prepaid. Annual subscription, $3.00.)

some have stated that what is improperly called "neurasthenia" is not a disease *per se*, but really a symptom complex of ductless glandular origin and that the adrenals are probably the most important factors in its causation. Campbell Smith, Osborne, Williams and others, including the writer, have directed attention to the importance of the adrenal origin of neurasthenia (though a pluriglandular dyscrasia is practically always discoverable), but so far this is not understood as well as its frequency and importance warrant.

A few quotations from the literature will firmly establish the importance of this angle from which to study this common and annoying symptom complex. Quoting from the *Journal A. M. A.* (Dec. 18, 1915) : "The typical neurotic generally has, if not always, disturbance of the thyroid gland. The typical neurasthenic probably generally has disturbance of the suprarenal glands on the side of insufficiency. The blood pressure in these neurasthenic patients is almost always low for the individuals and their circulation is poor. A vaso-motor paralysis, often present, allows chillings, flushings, cold or burning hands and feet, drowsiness when the patient is up, wakefulness on lying down and hence insomnia. There may be more or less tingling or numbness of the extremities."

Again, Kinnier Wilson in his monographs on "The Clinical Importance of the Sympathetic Nervous System" makes the following pertinent remarks: "Many of the common symptoms of neurasthenia and hysteria are patently of sympathetic origin. Who of us has not seen the typical irregular blotches appear on the skin of the neck and face as the neurasthenic subject 'works himself up into a state'? The clammy hand, flushed or pallid features, dilated pupils, the innumerable paresthesias, the unwonted sensations in head or body, are surely of sympathetic parentage. In not a few cases of neurasthenia symptoms of this class are the chief or only manifestations of the disease. Here, then, is a condition of defective sympatheticotonus; may it not have been caused by impairment of function of the chromophil system? . . . There does not appear to me any tenable distinction between the asthenia of Addison's disease and the asthenia of neurasthenia. Cases of the former are not infrequently diagnosed as ordinary neurasthenia at first. It is difficult to avoid the conclusion that defect of glandular function is responsible for much of the clinical picture of neurasthenia."

Later this same author makes the following apothegm: "Sympathetic tone is dependent on adrenal support, and until the glandular equilibrium is once more attained sympathetic symptoms are likely to occur."

SECTION IV. CHAPTER 6

THE DISORDERS OF THE PITUITARY BODY

The study of the various phases of endocrinology seems to have advanced in waves; and our knowledge of the clinical and physiological relations of the hypophysis or pituitary body is a good example of this. Thirty years ago quite an interest was aroused in this remarkable gland by the publication of Marie's classical study of the pathology of acromegaly and his correlation with it of disease of the pituitary gland. Nearly ten years later—in 1894—a greater wave of enthusiasm and interest was launched by Sir Edward A. Schaefer who made the discovery that the pituitary was a gland of internal secretion. Numerous investigations were initiated by this report, many of which have added materially to our knowledge of this subject.

The third greatest wave of all must be connected with the name of Harvey Cushing, and this has brought us to the present high tide of knowledge of the subject, for, thanks to the results of the years which Cushing has spent in investigating pituitary disorders, the profession is better able to realize the comparative frequency of affections of this gland.

Cushing's monograph, "The Pituitary Body and Its Disorders," has been called the most complete and useful monograph in English; and the numerous publications of reports of his work and that of his associates include the major part of our present knowledge on this subject.

Physiological Considerations. An appreciation of the essentials of the physiology of this gland, its interrelation with the other endocrine organs, and its influence upon the activities of the body, will enable us to detect the several results of functional pituitary dyscrasia during their early stages, before such obvious and serious changes as those present in acromegaly have established themselves.

It must be recalled that structurally the pituitary gland is divided in three parts: the largest anterior lobe being

a typical glandular structure; the much smaller posterior lobe having the histological appearance of nervous tissue, while the very small connecting portion, usually called by its Latin name *"pars intermedia,"* is made up of a mixture of both kinds of these cells. Each of these portions produces one or more chemical substances or hormones, the functions of which are not fully understood. Without going into detail, it may be stated that the anterior lobe produces a hormone which regulates the growth of the body. This was isolated recently by T. Brailsford Robertson at the University of California, and has been called by him "tethelin." In both physiology and organotherapy this substance promotes growth, especially that of bone and connective tissue; and it is expected that many useful advances in organotherapy will follow the clinical-experimental study of preparations of the anterior lobe of the pituitary.

From the posterior lobe there is secreted, presumably directly into the cerebro-spinal canal, a series of hormones which play an important part in the control of metabolism, especially that of the carbohydrates. They also influence in some subtle way the sympathetic nervous system quite similarly to the chromaffin hormone from the adrenals. Much clinical use has been made of the extract of the posterior lobe, and undoubtedly it exerts a very wonderful pharmacological influence upon unstriped muscle and particularly upon the uterus in labor. A diuretic hormone of considerable activity is also produced in this gland, some saying that it arises in the *pars intermedia* and others in the posterior lobe.

The pituitary lobe as a whole is very intimately connected with sex development as we shall shortly see; and is able to assist the thyroid and gonads vicariously when this becomes necessary. These complex relationships complicate the study of the subject, and it might just as well be stated right here that it is not a simple task accurately to differentiate between the results of deficiencies of these endocrine glands, for their relations are so intimate that it is quite impossible for one to be affected without some chemical reflex influence being brought about in the work of most or all of the others; and as these glands seem to exert a compensatory influence upon the work of those glands with which they are correlated, it is often difficult to determine the original gland at fault in a given case, and unless this is done, suitable treatment, organotherapeutic or otherwise, may be impossible.

We have just noted that there is a great functional difference between the parts of the pituitary. Like several other endocrine organs it is a dual one, with differing structure and physiological powers; and it is possible that clinical manifestations due to affections of one lobe may differ very materially from those due to disturbance of the other. An attempt to facilitate a differentiation between the disorders of the two lobes will follow the consideration of disease of the whole gland.

Dyspituitarism. When disorders of the pituitary gland are the result of tumors, cysts or intracellular disturbance, there may be varying secretory changes. On the one hand, pressure due to the growth may prevent the normal secretory activity, while, on the other hand, the enlargement may be a pure hyperplasia with markedly increased function until the limitations of the sella turcica—the bony cup above the sphenoid bone in which the pituitary rests—cause a secondary hypofunction. Such cases are termed dyspituitarism, since varying results are produced. In fact, many individuals suffering from pituitary excess, have at the same time evidences of pituitary insufficiency, secondary to the original trouble.

Dyspituitarism, then, is pituitary secretory dyscrasia and may include the pure hypo- and hyper-function and all grades between them and combinations of them. By careful study it is often possible to decide which disturbance is predominant and also which is the original disorder. A diagnosis of "dyspituitarism" is good; but to qualify this and go further into the genesis of the disorder, is much better.

Pituitary Insufficiency. With the fundamentals previously outlined in mind, we can expect marked changes in the metabolism as a result of insufficient activity of the pituitary gland. The most common result of insufficient function —hypopituitarism—is an undue increase in the deposit of fat which later may become a serious obesity, a condition which is probably due to the marked increase in the tolerance for carbohydrates usually found in hypopituitarism, and the abnormal desire for food and especially for sweets with which this is quite often associated. It is not uncommon to find patients in this class eating ravenously with appetites far beyond the usual.

The cellular activities are generally reduced and the temperature is subnormal, movements slow and somnolence is a prominent symptom. Parenthetically, Cushing and his

associates have remarked that hibernation in certain animals seems to be a physiological hypopituitarism. Lassitude, torpidity and drowsiness are often the first appreciated symptoms. (Some years ago I saw a case with Dr. W. W. Roblee at Riverside, who would fall asleep during meals or in the middle of a sentence; and who, by the way, improved very much under pituitary medication.) Sleep is not always refreshing and tiredness is a usual complaint.

This reduced oxidation is probably due in part to an associated thyroid insufficiency. The urinary solids are reduced, but the amount of urine is often increased; and it is now believed that the majority of those suffering from extreme polyuria, or diabetes insipidus, really have a form of pituitary disease. According to Motzfeldt and others, the lesion is in the posterior lobe, and the functional changes are on the side of hyposecretion.

There are well defined and almost pathognomonic retrogressive changes in the sex organs and functions. The syndrome described by Fröhlich and Bartels—the so-called "*dystrophia adiposo-genitalis*"—is due to hypopituitarism, the adiposity being marked and the sex-changes characteristic.

The age at which these conditions assert themselves naturally causes variations in the manifestations. When pituitary insufficiency is present in childhood or early youth, the developmental changes are more marked. The stature is small and skeletal growth is stunted. Genu valgum is quite common. The fingers are frequently tapered and considerably shortened, with a stubby appearance. Acromicria, i. e., unusually small hands and feet, has been noted by Timme, though this is rare compared with the corresponding opposite (acromegaly) in the opposite condition. The epiphyses may remain ununited and it is well in cases of reduced stature to have Roentgen pictures made of a hand, so that if defective epiphyseal growth is still present, there is hope for comparatively successful results from suitable organotherapy. On the other hand, in dwarfs showing fully united epiphyses there is little hope that the most effective therapeutic measures will increase the stature.

Temperamentallly, children with hypopituitarism are dull, apathetic, backward in their studies and easily discouraged. They often have difficulties with their playmates and lack both self-reliance and self-control.

The abnormalities of sex development are among the most typical results of pituitary insufficiency. The external geni-

tals are small, the pubertial growth of hair is sparse or absent. There may be either cryptorchidism or infantile uterus with impotence or amenorrhea. The menses appear late or not at all, and if the amenorrhea is not complete, the flow is scanty and irregular. The breasts often become extremely large due both to the adiposity usually present and to the reduced gonad activity. A peculiar and quite constant finding is a tendency to development which simulates that of the opposite sex, especially in the male, in whom the pubic hair line is straight and the contour of the hips and chest quite female in type.

The head is often small and the face unintelligent, and the distance between the eyes narrowed. The teeth are usually malformed and broad. The skin is dry and soft, and, compared with the dry, rough skin of hypothyroidism, is quite smooth to the touch, and wrinkling of the skin, especially on the backs of the hands, with deep cutaneous furrows surrounding each digit, is mentioned as a characteristic feature by Boston. Perspiration is much reduced, even in hot weather and during exertion.

When hypopituitarism is acquired after maturity it is often the result of syphilis, and the developmental changes just enumerated are not present. Here, however, there is anaphrodisia and sexual atrophy, obesity which may be extreme, with difficulty in locomotion and work, with a natural tendency to laziness and lethargy which further increase the asthenia and deposition of fat. Occasionally the fatty deposits are painful on pressure and are very similar to Dercum's disease or *adiposis dolorosa,* a condition which is probably of both pituitary and thyroid origin. This adiposity causes difficulties with the heart and breathing and edema may supervene due to fatty pericardial involvement.

Asthenia is the rule, irrespective of the extent of the obesity, and the unstriped muscles seem to be affected equally with the voluntary muscles, hence constipation is common and the bladder walls may be unduly weak with incontinence. The heart action is weak and the pulse slow and of reduced volume. The blood pressure is low, ranging from 100 mm. Hg. to as low as 50 mm. or less. The circulation is poor, the extremities are cold and sometimes edematous late in the day, and occasionally the skin exhibits the mottled appearance referred to in the previous chapter. Several authorities have noticed epilepsy as an accompaniment of hypopituitarism. Just what is the relationship we have yet to learn, but several writers, including

Cushing and Engelbach, have remarked that pituitary feeding caused a decided benefit to the epileptic manifestations as well as those which are more generally recognized as of pituitary origin. The therapeutic side of "endocrine epilepsy" is an important and seemingly hopeful subject and is considered further in Chapter 2 of the following section.

Hyperpituitarism. The start toward our present knowledge of the conditions associated with pituitary excess (hypertrophy and secretory activity) was made in the report of several cases in 1886 by Pierre Marie. He called the syndrome "acromegalia" because of the usually large hands and feet which were a prominent part of the clinical syndrome. A comparison of the manifestations of increased pituitary secretion would be expected to show diametrically opposite findings to many of the hypopituitaric conditions above. For example, children with hyperpituitarism are large for their age, tall and bony framed. Their eyes are wide apart, the face is broad, the cheeks prominent and the jaw square and large. The condition of the facial bones is generally called prognathism. The teeth many times are large, broad and irregularly spaced.

Such individuals have large hands and feet, with long fingers and toes and an unusually early epiphyseal union. The hair is usually profuse, exhibits a tendency to grow low on the forehead, well up on the abdomen and, occasionally, hypertrichosis is present. The axillary and pubic hair comes unusually early and is always excessive. The skin is thick, harsh and sometimes puffy. The sweat glands are usually active.

The sexual development is excessive and in early cases precocity is to be expected and sexual irritability may be marked. The sympathetic system is well developed and highly sensitive. Hyperpituitaric individuals are often bright and keen and very excitable, though they lack the power of concentration and are indecisive. Temperamentally, they are often irritable, distrustful, petulant and "difficult." They do not sleep well and insomnia is progressive as the glandular hypertrophy causes the local symptoms which will be referred to shortly.

The metabolism is plus and much accumulation of fat is rare. There may be a slight increase in the temperature, and the urinary solids are often increased. The tolerance to carbohydrates is reduced and the "carbohydrate tolerance test" is positive with 25 or 50 grams of sugar and not infrequently glycosuria is a symptom of hypopituitarism.

A urinary test for dyspituitarism is thus made possible. The high tolerance for sugar is usual in hypopituitarism. This may be easily demonstrated by giving measured, increasing amounts of sugar or, preferably, levulose, and noting how much may be taken without glycosuria. Often as much as 250 grams can be eaten (Cushing reports a case in which 450 grams was taken) without a trace of glucose in the urine passed during the next few hours thereafter. On the other hand, in the opposite secretory condition—hyperpituitarism—there is a very low sugar tolerance, and not infrequently there may be glycosuria.

The pulse rate is occasionally increased, though not very rapid; but the blood pressure may be high, ranging from 150 to 180 mm. or more.

Both gigantism and acromegaly are the result of hyperpituitarism; but in the former instance the dystrophy has commenced before ossification of the bones has taken place with a resultant increase in length principally. In acromegaly, i. e., hyperpituitarism after full development, the bone changes tend to thickness, hence the prognathism, protruding forehead and "heavy" facies, and the kyphotic spine not uncommonly seen.

Neighborhood Symptoms. When the secretory disturbances of the pituitary are coupled with hypertrophic changes, a series of localized symptoms is caused which are of a wholly distinct character from those due to chemical changes—the pressure or neighborhood symptoms. These are ultimate results and are practically always accompanied by changes in the size and conformation of the sella turcica which can be seen and even measured by roentgenography.

Unfortunately these pressure symptoms are often the first indication that we have dyspituitarism to contend with, and they are practically seen only in advanced cases. Under such circumstances we can expect to find supplementary evidence of the cause of the trouble by looking for the systemic chemical changes of pituitary origin which have already been enumerated. These localized symptoms are often so serious as to call for cerebral decompression and curative treatment is practically hopeless: while the general metabolic disturbances previously mentioned often may be favorably affected by persistent organotherapy.

To quote a statement from Cushing: "It is particularly important that we should learn to recognize these clinical expressions of hypophyseal disorder in the absence of brain

tumor symptoms or radioscopic enlargement of the pituitary fossa, in the same way that it is important for us to recognize thyroid disorders unaccompanied by gross evidence of change in the configuration of the gland."

Neighborhood symptoms may be roughly divided into two classes: Immediate (local) and intracranial (general) pressure effects. In the former we look for the results of pressure on the structures in contact with the mass; while in the latter, those found in any brain tumor—due to the increased intracranial pressure.

Among the former symptoms are well marked eye symptoms such as bitemporal hemianopsia (blindness of the outer temporal fields of vision) due to pressure on the optic chiasma. This usually first affects color only and later form. In more advanced cases, when the tumor extends beyond the sellar edges, squint results, due either to pressure on the sixth cranial nerve (internal strabismus) or the third cranial nerve (external strabismus). As a result of still more extensive involvement, there may be pressure on the crura cerebri and disturbances of gait with a positive Babinski sign. Certain epileptoid attacks, the so-called "uncinate fits" are occasionally seen and are probably due to pressure upon the uncinate gyrus. The relationship of epilepsy and pituitary disease is interesting and bids fair to offer a part of the solution of this problem.

Before the last of these pressure symptoms have been caused, general intracranial symptoms will have supervened. These consist chiefly of a severe intractable headache, paroxysmal in character and often affecting both temples, with vertigo, vomiting (often of the projectile type) and failing vision with later choked disc (papilloedema) and progressive destruction of the visual fields and ultimate optic atrophy.

Differentiating the Lobes Involved. It is rare that we find dyspituitarism of a single lobe, though it is possible. It is not unusual, however, to find predominating symptoms indicating that the principal trouble is in one of the lobes. If we bear in mind the varying physiological activities of the different portions of the hypophysis we will expect to find anterior lobe disorders more frequently accompanied by changes in growth and skeletal development. We have seen that with hypersecretion early the result is giantism, whereas later in life, acromegaly is the result. On the other hand, hyposecretion retards the growth and if it comes early the result is infantilism, while later it brings about

retrogressive changes in the sex organs and manifestations.

Dystrophies of posterior lobe origin are quite different, since they account for metabolic changes which cause the adiposity and increased carbohydrate tolerance found in hypopituitarism, while the excessive secretory activity of the posterior lobe produces a relative carbohydrate intolerance with glycosuria and increased metabolism and loss of weight.

Commonly both lobes are affected simultaneously, though the effects of one lobe may be more prominent and may change at different stages of the disease. Fröhlich's syndrome, for instance, is evidently due to a secretory deficiency of the whole gland.

The Cause of Pituitary Affections. Etiology is often of great service in making a therapeutically useful diagnosis. In the estimation of the writer syphilis is the chief cause of dyspituitarism, and while heredity is an evident factor, syphilis in parents and grandparents may have left an intangible susceptibility. The Wassermann test is very useful here.

New growths of the hypophysis, other than gummata, are common etiological factors, the causes of which are still altogether unknown. Early organic changes in the bony pituitary fossa may restrict the proper development of the growing gland. Brain tumors, either adjacent to the pituitary or remote from it, may cause dyspituitarism by increasing the intracranial pressure and the pituitary symptoms may entirely disappear following decompression.

It has also been suggested that as the posterior lobe is supposed to secrete into the cerebro-spinal canal, changes in the intraspinal pressure may cause pituitary disorder.

SECTION IV. CHAPTER 7

ENDOCRINE DYSFUNCTION OF THE MALE GONADS

"Removal of the sexual glands produces profound changes in the organism, evidenced as alterations of bodily physique and of temperament. If the extirpation is made at an early period in life, the so-called secondary sexual characters may fail to exhibit themselves in the usual manner, and thus occasion the retention of infantile characteristics in place

of typical features of adult form and behavior. There is reason to believe that we may properly speak of 'genital hormones' at the present time, in explanation of the undoubted chemical correlation exerted by the genital glands on other parts of the reproductive apparatus as well as on the organism in general. At any rate, the secondary sexual characters must be associated with the influence of chemical substances produced by the ovary and testis, respectively. Castration after puberty cannot modify profoundly the development of structures like the skeleton, which are already completed; but it may unquestionably bring about obvious structural and even functional changes which can be determined by careful observation."

The foregoing paragraph, quoted from an editorial in the *Journal of the American Medical Association* (May 13, 1916), is a fit introduction to my brief consideration of this subject. The "genital hormones" from the testes, like hormones from other glands, may be produced in insufficient quantities (hypogonadism) or may be absent (agonadism). Varied functional as well as structural changes result. They are not very difficult to diagnose; but the establishment of the cause is another matter.

Perhaps the endocrine dysfunction of the testes does not require a comprehensive study, for we are better acquainted with the results of increased or decreased physiological activity of these glands. An early hypogonadism virtually means essential infantilism, sexual insufficiency and maldevelopment as cryptorchidism and total absence of the testicles.

Essential Infantilism. There are several clinical forms of organic gonad disorder: Infantilism is the condition in which the glands are poorly developed or absent. Here the results are much the same as in hypo-ovarism, the form and function are changed, the bodily growth is altered and the secondary sexual characteristics which normally should show themselves at puberty do not materialize.

The testicles are very small, the scrotum atrophied and the penis short and incapable of erection. Infantilism may vary in degree, and developmental changes are not always necessarily accompanied by absolute inactivity of the interstitial cells of Leydig. In this case, there eventually may be possibilities of sexual desire and azoöspermia may be absent. The cause may be inherent in the sex glands themselves, but usually is due to other endocrine difficulties which are discussed elsewhere.

Cryptorchidism. The developmental anomaly known as cryptorchidism, also known as "undescended testicle," is not rare; but cases with permanent cryptorchidism are very uncommon. There may be two forms, the abdominal and the inguinal. Occasionally this condition is accompanied by testicular maldevelopment with lack of all the functions dependent upon proper activity of the Leydig cells. Again, despite complete burial of the testes, they may be functionally active, in which case there is sterility in individuals none the less potent, the sterility being purely mechanical rather than functional. Such cases obviously are not subject to the same degree of asexualism as in pure infantilism or in castrates.

I have seen many endocrine dystrophies of the gonads which were not essential, i. e., they were related to pituitary or thyroid disturbances (insufficiency) and the matter is mentioned in the chapters devoted to these subjects respectively. I recall a case of a defective boy of ten with cryptorchidism to whom I recommended my *Antero-Pituitary Co.* I explained to the mother that I did not believe that there were no testes at all but that they had not descended. I also said that they would not likely develop at puberty if they were permitted to remain in the canal and that surgical treatment should be given before then. I hinted (ever so carefully), that the medical treatment (organotheraphy) might help; and to the surprise and delight of all, the testes both came down after nine weeks of this treatment with nothing added but some simple dietetic admonitions. The only sad thing about the case was the comment of a colleague that it was "probably a coincidence!"

Eunuchoidism. The condition known as eunuchoidism is presumed to be an acquired disorder of the interstitial cells of Leydig, and those with this disturbance are quite similar in functional incapacity to a castrate but without the absence of the testes. Here there is complete functional loss of the sex principle later in life, so that the more marked manifestations of infantilism are not present.

The eunuchoid is so named from the similarity in form to the eunuch or castrate, and in addition to the retrogressive changes in the secondary sex characteristics—avirilism, reduction of facial, axillary and pubic hair, genital atrophy, etc., there is an acquired corpulency due to the loss of the powerful oxidizing principle produced in the interstitial cells. A subnormal temperature is the rule in these individuals, and it has even been suggested that this common associate

finding in senility (or presenility) is of gonad origin.

Eunuchoidism may be due to disease or be a spontaneous hormonically produced disorder, and it is accompanied by a loss of the factors dependent upon active sex-gland function—assertiveness, courage, animation and sexual power. The ergograph has been effectively used to demonstrate the actual loss of energy and power following disease or injury to the gonads, as well as to show the energizing influence of suitable organotherapy or the more recent work by Lydston and others, with sex gland transplantation.

Functional Sexual Disturbances. Many a monograph has been written on this subject, and it is far too large to be considered fully here. Impotence, presenility and senile testicular insufficiency always have been a subject of perennial interest. From a diagnostic standpoint, the principal symptoms are lack of sexual desire and power and "sexual neurasthenia" with its innumerable manifestations. According to Williams, functional testicular disorders, especially on the side of deficiency, are known to cause general depression, hysteria, hypochondria, melancholia and also digestive disturbances.

It may be well to recall that the fundamental basis of modern organotherapy and the "fillip" which restarted an interest in the age-old study of organ medication was the use by Brown-Séquard of testicular extract on himself. The dynamogenic influence of this sort of treatment then, as now, is unquestioned; but for various reasons it has never assumed the importance that it really deserves. It is given some consideration elsewhere in the chapter entitled, "The Hormones in Impotence" (Sec. V, Chap. 21).

Senility and Presenility. According to Lorand, "A man is as old as his internal secretions," and the condition we call "age" is nothing but a gradual waning in the endocrine functions with the accompanying reduced cellular activity and unavoidable toxemia, which finally overburdens the body and allows the vital organs to fail. The condition we call "senility" is merely old age, and "presenility" is a premature aging which may range from the remarkable condition known as progeria (infantile senility) to a premature loss of virility. This capacity, the maturity and strength of manhood, is bound up in the powers of procreation; and when this capacity wanes, whether from age or disease, senility exists—or avirilism. This is accompanied by loss of strength, deficient oxidation, malnutrition, especially of the skin and appendages, and resulting in wrin-

kles, old appearance and the loss of hair and, above all, of the endocrine and spermatogenic functions of the testes. This is a natural consequence of the ravages of time, just as it is a premature consequence of the ravages of lust. In both instances, the essential sex glands are functionally inactive, and there is present the same hypogonadism that we find in the pathological conditions previously enumerated.

The diagnosis need not be discussed further, and its successful control through a mythical "*Elixir Vitae*" has been the goal of many from time immemorial and from Ponce de Leon to the present day. Hypogonadism may be amenable to organotherapy, even in elderly men, and the fundamental principle of homostimulation (see Sec. II, Chap. 2) holds good "in proportion to the responsiveness of the glands thus stimulated." It is a broader matter than the gonads alone, as the thyroid, pituitary and other endocrine glands all play their part. Senility, then, is hypocrinism rather than hypogonadism alone; and if we must treat it, it should be treated in the larger sense; and when organotherapy is in mind it should be preferably *pluriglandular therapy.*

Undoubtedly there is such a condition as hypergonadism; but in most cases we have to meet, the origin is psychic and usually beyond the control of ordinary medical treatment. From a diagnostic standpoint, it is not difficult to determine.

SECTION IV. CHAPTER 8

THE DIAGNOSIS OF OVARIAN DYSCRINISM

The ovaries produce at least two distinct internal secretions, one from the corpora lutea and the other from the interstitial cells or stroma. The differentiation of the hormonic value of these substances is difficult, but, broadly speaking, the luteal hormone is chiefly concerned with the determination and production of menstruation and probably the growth of the sex organs, while on the other hand, the stromal hormone is chiefly concerned in the regulation of the nutrition of the uterus and is believed to exert an inhibitory action upon the menses. Some believe that the luteal hormone also sensitizes the uterus to prepare it for

pregnancy and the development of the placenta. It is suggested that these two hormones, acting in alternation, bring about the entire phenomenon of menstruation.

The biochemical basis of femininity is much more important than either the psychological basis or that dependent upon the nervous system. The hormones transcend in importance all other factors in the regulation of the chemistry of the body and, therefore, of the chemistry of the reproductive organs. Hence, derangements in the endocrine glands, particularly the gonads, spell disturbed metabolism, altered nutrition and modified sex conditions. Most certainly the ovaries have much more to do with remote nonsexual factors than is usually believed; and while it may not be known to which portion of the organ the effects may be credited, it is certain that the ovaries are definitely concerned in the subtleties of cellular chemistry and have much to do with the maintenance of the calcium balance.

The Influence of the Associated Glands. The fact that the ovarian internal secretions are so intimately connected with those of other glands, notably the thyroid and pituitary, makes it rather difficult to set down accurately the results of ovarian dysfunction since the symptoms may not necessarily be purely ovarian but rather due to a pluriglandular manifestation which includes factors not of ovarian origin at all. For instance, according to Osborne, a woman castrated during menstrual life generally adds weight, not only because of the cessation of the loss of blood, but also because of the loss of the ovarian secretion and *"of the coincident lessening of thyroid secretion and perhaps of pituitary secretion."* The supreme importance of these relations is emphasized in another quotation from the same authority (*N. Y. Med. Jour.*, Sept. 1918): "The thyroid is typically a female gland, entering constantly into the woman's sexual life. Menstruation cannot possibly occur without the activity of the thyroid. Too much thyroid secretion may cause profuse or too frequent menstruation. The thyroid hypersecretes at each menstrual epoch and during pregnancy, and many disturbances of the menopause are due to too much or too little thyroid secretion. . . . All through female life, the thyroid secretion is of constant importance, and normal ovarian and uterine functions cannot occur without normal thyroid function. In female cretins, the genital organs may develop, but do not function."

Another phase of the thyro-ovarian relationship must be mentioned, under the circumstances. The ovarian secretion

reciprocally stimulates the thyroid, and at the change of life the absence of hormone stimulation from the ovaries may cause a thyroid insufficiency, with the result that the woman adds weight more or less rapidly, the skin becomes dry, she may be sleepy and more or less mentally apathetic, and in general she shows the signs of myxedema. According to Osborne, "this (menopause) is a period of life when myxedema is most frequent, by far the majority of all non-operative myxedematous cases occuring in women and in the decade of forty to fifty." Hence it can be seen, both from the standpoint of cause as well as of effect, that ovarian insufficiency is so definitely connected with the thyroid function that the symptoms are really also the symptoms of thyroid insufficiency, and *vice versa.*

From the standpoint of diagnostic endocrinology, the ovaries are subject to three forms of functional disorder: (1) deficient secretion, (2) excessive secretion, and (3) perverted secretion. The results of these, limited as far as possible to the ovaries and not to pluriglandular syndromes in which the ovaries play a part, will be considered briefly and the diagnostic essentials outlined here.

Symptoms of Ovarian Insufficiency. The outstanding manifestation of hypo-ovarism is amenorrhea in varying degrees from a complete absence of the menses, through irregular menstruation to delayed or scanty menstruation, frigidity, sexual apathy and sterility. Equally important is dysmenorrhea in its various manifestations. The underlying disorder may be early and spontaneous in origin, or it may be a later, acquired condition; i. e., the change may be initiated sufficiently early to prevent the normal development and growth dependent thereon, or, on the other hand, ovarian disease may supervene after maturity with an obviously modified train of results. The former condition naturally implies a wider and more fundamental symptomatology, for the changes of puberty are purely of endocrine origin and the ovaries are among the principal agencies in bringing them about. The results of early ovarian insufficiency are combined and generally known as "infantilism." The usual findings include delayed or arrested growth of the body as a whole and of the reproductive organs in particular. The breasts may be small and undeveloped, though not infrequently this does not appear to be the case, especially when there is plenty of fat in the tissues. The hips are narrow. The pubic and axillary hair is scanty or absent; and the psycho-sensory sex evidences are diminished or absent.

The later onset of ovarian insufficiency is not accompanied by such well marked evidences, at least as far as physical development is concerned, for obvious reasons; but the functional changes are usually clearly discernible. Since the growth of the myometrium and, in fact, the pelvic circulation and reproductive development are under hormone control, in case of ovarian insufficiency the uterus may be expected to be infantile (or "senile") and the adnexa undeveloped or atrophied. Where this is acquired later in life, genital atrophy is to be seen as a shrinking of the internal and external genitalia. The labia majora diminish in size, while the labia minora are slender and insignificant and may disappear entirely. The introitus narrows and tends to become valve-like, and the modified vaginal membrane is thin, pale and mottled, later becoming tough and unyielding. The vagina contracts and obstructing bands may be formed, while the cervix shrinks and its lumen tends to close.

Typical Functional Ovarian Insufficiency. A more or less typical case of deficient ovarian functioning may be outlined: The patient complains of uncomfortable sensations, such as pelvic heaviness, vague nervous manifestations and a feeling of general malaise of varying degree for a longer or shorter time prior to each expected menstruation. Delay is the rule. Irregularity of onset and a scant flow are customary. During the "over" period she may and indeed often does suffer from severe colds, an old tonsilitis lights up, headaches of quite decided severity are common, boils or acne are sometimes found and, in fact, the patient is so tired and below par at that time that during it any latent condition may become aggravated because of the temporarily lowered resistance. When the menses do show up and get properly started, these troubles begin to disappear—until the next premenstrual delay. And so on. The delayed menstruation favors a condition of neurasthenia and worry which adds to the aggravation all around.

It is easy to see that neuroses are common in those suffering from dysovarism. Many sympathetic nervous disorders, well defined as well as vague, have a large ovarian element in their make-up. Many cases called "neurasthenia" and many "reflex" mental and physical ills are connected in some direct or remote way with the menstrual ovarian function. Occasionally these develop into psychoses, which may or may not respond to organotherapy. The fact that they are related in some way to ovarian physiology (or pathology), that they are influenced by conditions involving

menstruation, intercourse, pregnancy or psycho-sexual matters should be proof enough. The best kind of conviction, however, comes from developing a supposition into a reality by initiating the right kind of treatment—in this instance, in my estimation, pluriglandular therapy—and controlling the manifestations, a thing that has been done times without number.

Menopausal Difficulties. When hormone production ceases at the "change of life," the delicate hormone balance, the mechanism of which has depended upon ovarian hormone activity for approximately thirty years, sometimes is sadly deranged, causing considerable disturbance in the work of the other ductless glands. The extent of this trouble depends very largely (1) upon the previous ovarian hormone production, and a person who had been accustomed to quite considerable ovarian activity might react less favorably than where this activity had been less; (2) the rapidity of the completion of this function (a sudden menopause, like the "surgical menopause," is likely to be more severe than when the transition is more gradual), and (3) the sensitiveness of the associated glands, especially, in my estimation, the adrenal glands, which, it will be recalled, are unusually sensitive to toxemia, acidosis and emotional factors.

The organic changes are too well known to require reiteration here and include most of the retrograde anatomical changes previously mentioned. The chief symptoms of this condition are of a circulatory character, due in all probability to the indirect influences upon the adrenal glands. Reflex troubles are often found, the most common of which is headache, probably of circulatory origin, although more than one case of post-climacteric headache has been known to be due to pituitary dysfunction, resulting, in all probability, from an attempt of the pituitary gland to make up for the ovarian deficiency—a "friendly" activity which is not always best for the patient. Flushes of heat, fleeting and indefinite pains, sensory disturbances in various localities, pelvic fullness due to congestion with frequent periods of menorrhagia, sympathetic irritability, on the one hand, or melancholia and depression, on the other, make up a symptom-complex which is often called neurasthenia but which is nothing in the world but dyscrinism—a disordered function of the glands of internal secretion due to the imbalance between the ovaries and the other glands.

Functional Sterility. With the changes enumerated above, one would expect to find sterility, and this, of course, is the

rule at the menopause. Indeed, the endocrine glands have much to do to enable the uterus to house an impregnated ovum seeking a lodging place, and many cases of presumably normal ovulation, with or without menstrual difficulties, are sterile because the ovum is lost. Indeed, this form of sterility may be the only sign of ovarian insuffiency, and there certainly must be many early abortions in which the cause is not so much defective ovulation (syphilis having been ruled out) as a difficulty in the proper implantation of an apparently normal embryo, a function which is now conceded to be made possible through hormone influences and which, fortunately indeed, occasionally may be remedied by suitable organotherapy.

The endocrine aspect of sterility and the organotherapeutic remedying of this condition are subjects which are being given close attention at this time, and within the last year several very comprehensive articles have been written, perhaps the most interesting of which is by S. W. Bandler, of New York.

From my own standpoint, sterility, even of a most persistent character, is not nearly such an impossible condition as has been supposed. I have personally seen a number of cases in which every anatomical feature was normal—the chemistry of the vaginal secretion was ruled out as a factor —but there was a subtle dysthyroidism which was only discovered by the use of my thyroid function test (see Sec. IV, Chap. 4), and upon the initiation of a comparatively short course of suitable organotherapy, the desired impregnation occurred. With this thought in mind, it may be well to recall some things that have already been said about the thyroid, pituitary and ovarian functions. Myxedema and the less serious forms of thyroid insufficiency spell ovarian insufficiency, amenorrhea—and sterility. The typical pelvic findings in hypopituitarism are a functional ovarian insufficiency and, later, atrophy of the whole genital system. There is also a pituitary element in sterility. Possibly other glands are also involved, but it is certainly true that the consideration of the "endocrine trinity of sex," the ovary, thyroid and pituitary glands, opens up a fertile field for the clinical treatment of many functional pelvic difficulties, including sterility, and attention is called to three chapters on ovarian disorders (Sec. V, Chaps. 5, 6 and 7), in which reference is made to two formulas, the one No. 4, *Thyro-Ovarian Co.* (*Harrower*) for the regulation of the ordinary disturbances of ovarian function, and No. 73, *Gonad-Ova-*

rian Co. (*Harrower*) (containing anterior pituitary substance in addition) for the more definite cases of sterility and sexual apathy, including those in which ovarian therapy and the thyro-ovarian formula have been tried for some months without a satisfactory outcome.

Over-secretion of the Ovaries. Excessive ovarian activity is not nearly so frequent as hypo-ovarism. Rarely in early life it may accompany pituitary disease, abnormal thymus atrophy or a pineal tumor, and as a result of the dyscrinism the ovaries may commence to functionate very early or abnormally. Cases are on record where the evidences of puberty were present at five years, and, from the standpoint of fecundity, while procreation may not have been possible, at least such cases were rightly classed as "precocious." For reasons that may not be always clear, psychic, endocrine or organic, the ovaries may function excessively, as a result of which those factors dependent upon ovarian function are increased, including sexuality, which may develop into all kinds of sexual perversion, and menorrhagia. This latter may be represented by too frequent menstruation or by an excessive flow at proper intervals. There may be varying degrees of pelvic sensitiveness and pain, with a sense of uncomfortable fullness in the lower abdomen due to congestion. This same circulatory derangement results in irritation of the external genitalia, and the sympathetic balance may be so badly disturbed that hysteria may be directly due to this disturbance.

The adrenal glands may be so excessively stimulated by this abnormal production of the ovarian hormone that they may be depleted, and following the condition of adrenal irritability and sympatheticotonus there may be long periods of adynamia and asthenia so common in certain ovarian cases. It should be remarked in passing that numerous other circumstances may be the cause of adrenal depletion; and the consequent asthenia, while accompanying other evidences of hyperovarism, really may be due to other remote causes. Functional hyperovarism is practically never existent without associated sexual neuroses, and it may include masturbation and nymphomania, even growing into "sexual insanity." Several years ago the writer suggested a therapeutic-diagnostic test which is well worth trying in hyperovarism. Functional menorrhagia and other conditions purely due to ovarian excess (not to new growths or to mechanical causes) are often modified by mammary organotherapy. Five to ten grains of desiccated mammary

gland given three times a day before meals have controlled the hemorrhage and pelvic uncomfortableness very nicely. At the same time this assists in establishing the functional basis of the disorder. (Parenthetically, the internal secretion of the mammary glands exerts an antagonistic action over that of the ovaries—see Sec. V, Chap. 9—as does that of the pancreas over the secretion of the adrenal medulla.)

Osteomalacia an Ovarian Symptom. One of the chemical results of hyperovarism is especially noticeable in osteomalacia. This lack of lime and softening of the bones is now known to be intimately connected with the glands of internal secretion and particularly the ovaries. Osteomalacia may be brought about directly by ovarian excess (and be remedied very largely by removal of a portion of the hyperactive glands just as the thyroid is removed, in part, in hyperthyroidism, etc.). In these cases, the disordered calcium metabolism is due probably to the abnormal excretion of the lime brought about by the undue ovarian stimuli. Blair Bell has shown by numerous experiments that the ovaries are an important factor in the regulation of the power of the organism to appropriate calcium; and the clinical experiences with osteomalacia seem to prove his contention. This condition is not usual in non-pregnant women as they do not have the great need for lime that is present during pregnancy; but since child-bearing causes a large demand for extra lime, softening of the bones may occur and is not uncommon in Italy, Austria and India. At one time, osteomalacia was routinely treated by oöphorectomy, but since Bossi, in 1907, first suggested the administration of an antagonizing hormone instead of ovarian removal, adrenal substance has been given with many resulting cures. More recently Blair Bell has directed the treatment of a series of cases in India, at long range, and at his suggestion the posterior pituitary principle has been given in osteomalacia with distinct benefit in a number of cases. This seems to indicate that osteomalacia is likely a pluriglandular disorder, the hyperovarism being coupled with hypoadrenia or hypopituitarism. This is undoubtedly the case and indicates a prospective method in hyperovarism where treatment is unavailing and operation inadvisable.

The Causes of Ovarian Excess. The first cause of hyperovarism is functional irritability due to the circulatory derangement accompanying pelvic inflammation or malposition of the uterus. Another common cause is connected with hygienic conditions of a personal nature, involving associa-

tions, reading and various sex circumstances. These two factors, mechanical and psychic, induce a condition of circulatory stasis which is equally the result of infections, uterine subinvolution and malpositions. This stasis is a common cause of ovarian disease which is first functional and later organic.

The Ovarian Element in Fibroids. A number of years ago, surgical removal of the ovaries was recommended for the control of the uterine fibroids and the accompanying menorrhagia. It is well known that the menopause frequently alters the symptoms of fibroid growths and causes a cessation of their growth or a reduction in size. Ovarian antagonism by the X-ray is a frequent recourse in fibroid menorrhagia; likewise, organotherapy opposed to ovarian hormone function reduces the symptoms.

All of these facts lend weight to the belief that uterine fibroids are possibly the result of hyperovarism, and, among others, Briggs, of Sacramento, believes that the exciting cause of these new growths and the accompanying hemorrhages is uterine hyperemia of ovarian origin and that the antagonistic effect of the mammary principle is helpful because of its anti-ovarian influence. Briggs reports a number of clinical experiences to establish his theory and states that in "a large majority of cases receiving mammary extract, the menorrhagia is effectively controlled and under its continued use large uterine fibroids often disappear, even during the early reproductive period." The mammary hormone probably antagonizes the follicular (stromal) hormone or inhibits its production and thus moderates or prevents an excessive menstrual molimen and its consequent hyperemia, menorrhagia and local nutritive disturbances. The effective dosage therefore would seem to depend on the degree of excessive ovarian activity—the greater this functional activity, the larger the quantity of mammary extract required to inhibit or antagonize it.

This conception of the cause and treatment of fibroids has been successfully carried out by many physicians (see Sec. V, Chap. 9, "The Control of Menorrhagia"), and the use of No. 40, *Mamma-Pituitary Co.* (*Harrower*) is recommended because each of the ingredients favors uterine depletion and encourages pelvic tone, while the mammary extract is a direct "anti-ovarian" remedy.

Organic Ovarian Disease. Local structural changes in the ovaries themselves are very numerous and they really form a third class of cases of ovarian dysfunction, for the exces-

sive endocrine activity is not so much an increase in the normal production of the ovarian hormones as the actual production of aberrant chemical substances from new growths or cysts in the ovaries. The frequency of ovarian tumors is responsible for this, the condition is differentiable from hyperovarism, and the clinical findings are irregular since this disorder may be accompanied by periods of ovarian excess or insufficiency. Occasionally there is produced in the ovarian tissue (either in the normal interstitial or luteal cells, or in those of the new growth) a toxic hormone of extreme virulence, and in comparatively recent German literature the term "ovarian poisoning" is found, denoting a vicious activity of diseased ovarian tissue with serious remote effects due to the poison produced there and secreted directly into the blood stream as are practically all the hormone-bearing internal secretions. The treatment, of course, involves the removal of the offending tissue.

Dysovarism may be the cause of alternate periods of amenorrhea and menorrhagia. Dysmenorrhea is the rule. Neurotic manifestations are quite usual, and some have reported insanity as one of the possible results of this variety of ovarian derangement, incidentally explaining some remarkable "cures" of insanity following surgery of the ovaries. Under certain circumstances an abnormal menopause virtually develops into a minor form of dysovarism, the varying symptoms being due to irregular periods of differing ovarian activity.

The most common symptoms of dysovarism are pain in the pelvis and severe asthenia. The extreme prostration and weakness is doubtless due to a superinduced hypoadrenia, and may be the outstanding feature of a case. In most cases, on bimanual palpation, the offending organ or organs frequently will be found to be nodular, irregular, enlarged and tender. Here again surgery is proper.

SECTION IV. CHAPTER 9

THE DISEASES OF THE THYMUS

Disorders of the thymus gland are not common, though they are undoubtedly more frequent than is supposed. There always has seemed to be an element of mystery about this gland, due possibly to the strangeness and suddenness

of deaths of thymic origin. However, this is being replaced, and we are now able to understand the thymus better than we did a few years ago.

As with the other ductless glands, we may find a cellular enlargement of the thymus with local symptoms due to pressure; or, on the other hand, there may be a change in the functional activities of the gland with varying effects upon the body as a whole. It is not generally conceded that the thymus is really a gland of internal secretion, although it influences metabolism and also the work of the other ductless glands in a manner very similar to other known endocrine glands.

It has been suggested that the principal function of the thymus is to produce lymphocytes, and Sajous, of Philadelphia, believes that any effects that it may exert upon metabolism, positive or negative, are due to these cells or their contents. Of course, it is quite possible that these blood cells carry within themselves certain chemical substances which are very closely allied to hormones, if not actually such.

Physiological Considerations. Most authorities consider the thymus as a temporary organ which reaches its height of development about the age of two, and retrogrades slowly until puberty, at which time it is supposed to disappear, though this opinion is not unanimous. Proof that the thymus is not a lymphoid organ alone is found in the intimate relation between the thymus and the metabolism of the mineral salts, especially of calcium and phosphorus; for when there is early or experimental thymus dysfunction the chief organs to suffer from the resultant chemical changes are the bones, muscles and, perhaps, the nerves, in the order named.

There is an abundance of evidence connecting the activities of the thymus with those of the gonads. It seems that the thymus antagonizes the action of the sex glands, and that increased thymus function, especially during the period of development, causes deficient development of the reproductive organs; while, on the other hand, deficient thymus activity may cause an increase in the growth and function of the gonads. At least we know that if the thymus does not retrograde in the usual manner at puberty there likely may be evidences of defective sexual development, and from this the conclusion is drawn that the study of the thymus should be a part of the study of all cases of deficient gonad function or development.

Another important clinical fact which indicates another physiologic intimacy of the thymus, is found in its relation to idiocy in children. It has been remarked that a large percentage of idiotic children have no thymus at all. Morel reports that of over four hundred idiotic children with normal thyroids coming to autopsy, over 75 per cent possessed no thymus. In passing, it is interesting to note that Klose has experimentally shown that thymectomy in dogs is followed by a gradual change in the mental powers until a condition whch he terms *idiotia thymopriva* is present. While this does not necessarily prove that athymia is the cause of idiocy, it is at least a very suggestive finding and one which has been well established by many investigators.

Thymus Insufficiency. Experimental proof is at hand to show that the removal of the thymus from animals causes a decided reduction of growth—dwarfism. It is not improper to presume that this holds good with children. At least there is a probable thymic element in dwarfism, and support of this is found in several communications which report benefit following thymus feeding in certain cases where the weight was low and the height reduced.

Certain nutritional disorders in children, notably marasmus, are quite commonly associated with thymic atrophy, and some interesting clinical proof of this is available. Deficient children, especially when there are disturbances in bone growth and development, should always be considered from the thymus aspect until definitely proved not to be suffering from hypothymism. Parenthetically my formula No. 2, *Antero-Pituitary Co.*, which is recommended in the treatment of defective children, contains an effective dose of thymus substance. (See Sec. V, Chap. 11.)

Naturally hypothymism is not to be expected in adults for the gland normally becomes inactive at or near puberty. However, individuals with thymus dyscrasias in childhood may retain certain chemico-nutritional disorders as a result of the previous disordered function of this gland.

The blood changes are not characteristic; but one frequently finds hypothymism accompanied by anemia and especially lymphocythemia. Reduced coagulability is also common and frequent bleeding at the nose may be the first indication of thymus disorder. Still another incidental defect has been connected with dysthymism. Browning states that there is a relationship between the thymus gland and stammering. While all cases with an enlarged thymus do not stutter, all stutterers will be found to have an enlarged

gland. This is denied by some, but is worth remembering. After all, success in the detection and treatment of ductless glandular disorders is attained by noting insignificant things.

One frequently notes a peculiar condition of hairlessness (especially of the head and face), and a yellowish, parchment-like skin in pluriglandular dyscrasias in which the thymus element is or has been prominent. Parenthetically it may be well to remark that Sajous suggests that the rare condition known as progeria or premature senility (in children), is really due to thymus disease.

Some of the findings in experimental and clinical work are sometimes contradictory, and the reason for this is due to the fact that the endocrine organs are so intimately connected with one another. At one time a certain hormone seems to be in the ascendancy, whereas at another, it is deficient. As an instance of this a case of presumed hypothymism with retarded growth and sexual development was treated with thymus substance for some months with a remarkable increase in height and general progress, though it must be recalled that theoretically the removal of the antagonism of the thymus (as in hypothymism), should favor functional gonad activity and the developmental and other results thereof.

Hyperthymism. Hyperthymism is not a common or easily diagnosed condition. It is rarely found unaccompanied by other ductless glandular disorders; indeed it is a disorder which one should be ready to look for mainly in connection with certain forms of thyroid excess. A number of reports indicate that one should carefully look for an enlarged thymus and evidences of its excessive activity in every case of Graves's disease, and particularly before surgical intervention is undertaken. After a careful search both of the literature and numerous unpublished hospital records, Matti collated 133 cases of sudden death in hyperthyroidism in which a post mortem examination had been held and in 98 cases, or 74 per cent, a hyperplastic thymus was found. Such records emphasize the advice just given regarding the relation of thymus disorder with Graves's disease.

A number of deaths have followed thyroid operations, due to thymus complications. Not a few times a share, at least, of the heart and nervous symptoms attributed to hyperthyroidism has been due to a concomitant hyperthymism. In this connection it must be emphasized that while an en-

larged thymus may be usual in such cases, there is no doubt that the degree of thymotoxemia may have little to do with the size of the gland.

Experimentally and clinically, excessive thymus function is accompanied by severe general nervousness, tremor and a rapid, irregular pulse. Thymotoxemia of this character may be amenable to roentgenization of the thymus area.

There is a somewhat rare thymus type of adiposity which is usually accompanied by lymphatic tendencies, and in which one often may find a well defined thymus area on X-ray examination. In such cases myasthenia is persistent and may disappear after suitable treatment—Roentgen or surgical.

In cases of thymus disorder one usually will find a considerable increase in the number of lymphocytes in the differential blood count, and this procedure is recommended not merely when thymus disease is suspected, but in the routine clinical diagnosis of Graves's disease.

According to Paltauf the characteristic features of hyperthymism are: (1) Hyperplasia of the various groups of lymph glands, tonsils, spleen, and, of course, the thymus itself (see status thymo-lymphaticus); (2) Lymphocytosis, the count being increased to 50 per cent or more (i. e., increased 100 per cent or more); (3) Cardio-aortic aplasia; (4) Maldevelopment of the genital glands and their adnexa; and (5) A pale, badly nourished skin with scanty hair and an exaggerated *panniculus adiposus*. It is fair to add that one rarely finds all these in a single case.

Diagnostic Points in Thymus Cases. Attention already has been called to the value of the Roentgen ray in the diagnosis of thymus disorder. An enlarged thymus occasionally may be percussed as a triangular area of dullness under the manubrium of the sternum, in some cases extending outward on either side a short distance. This area of dullness may move slightly upward on extending the neck by drawing the head well back. The base of this triangle is between the sternal ends of the clavicles, and the apex between the junctions of the sternum with the second and third ribs. Halstead has noticed that downward pressure on the sternum may produce a sense of suffocation in cases of this character, which differs considerably from the normal.

It should be recalled that there is such a condition as a sub-sternal goitre or an intrathoracic thyroid; but this may be differentiated by the somewhat higher position of the

enlargement and the fact that it moves with the trachea in the act of swallowing.

Hoxie has described a symptom-complex in which an enlarged thymus is accompanied by shortness of breath and discomfort in the thorax, and extreme muscular weakness. In several cases reported, the asthenia was quite the most prominent subjective finding. This is of special interest, as there seems to be clinical evidence that myasthenia gravis is in some way connected with the thymus. Tom Williams has reported a case of a man with this disease who was apparently cured by the administration of thymus.

Thymus Hyperplasia in Children. We have already discussed thymus enlargement and hyperactivity; but thymus hyperplasia in children deserves mention by itself. It seems to be a somewhat different clinical entity not uncommonly found in infants and children and, unfortunately, too often only at the autopsy table. Many times this hyperplasia causes no well defined symptoms and is altogether latent until sudden death, the so-called *"mors thymica,"* is the first indication that something was wrong.

In infants, where an enlarged thymus is present, the initiation of breathing may be a prolonged and difficult matter. The cyanosis present at birth may persist and the breathing may be difficult and stridorous. In such cases the outcome is often fatal after a few hours or days.

Dyspnea in children is probably the most marked symptom of thymus hyperplasia, and its presence should always cause a careful search for other associated findings. It may vary in degree, depending upon the pressure, from an insignificant stridor, worse on stretching the neck or drawing back the head, to a serious and alarming air hunger.

In such cases the general health is poor. The skin has a pasty, badly nourished appearance, not unlike that of cretinism. There may be vague respiratory symptoms due to tracheostenosis, which later may develop into a peculiar harsh and intermittent cough which is sometimes erroneously called a "tooth" cough, a "stomach" cough or, for lack of a better name a "nervous cough." This cough occasionally may be short and dry during the day and considerably worse at night. It is possible that the cough may not be due to pressure on the air passages, but to irritation of either the recurrent laryngeal or vagus nerves, although tracheal stenosis is the most usual cause.

Status Thymo-Lymphaticus. This disorder differs somewhat from thymus hyperplasia since it is evidently an ac-

quired condition and is more frequently observed in older children and young adults. It is a more complex condition, the hypertrophic changes in the thymus being accompanied by a general enlargement of the bronchial, mesenteric and other lymphatic glands. According to Hart, the existence of a true status lymphaticus has not yet been proved with absolute certainty. To him it appears that the swelling of the lymphatic apparatus represents a tissue reaction dependent on the thymus and which may show itself also in the lymphoid components of the thymus itself.

Adenoids and enlarged tonsils are usual, hence cases with a well marked adenoid facies and other evidences of lymphatic enlargement should be studied as likely cases of status lymphaticus and the thymus should be sought for and, if possible, measured. According to Bierring and others, inexplicable deafness has been found in a number of cases.

In the past, status thymo-lymphaticus commonly has been diagnosed after sudden and unexplained death. We are now better informed about the symptomatology of thymus dyscrasias, and with increasing frequency this condition is detected before extreme results show themselves and in time to treat the thymus with the Roentgen ray.

Individuals with status thymo-lymphaticus usually are of the flabby, semi-obese type, with a peculiar pasty appearance of the skin of the exposed parts. Pigmentation is occasionally seen, especially in cases of Graves' disease with thymus involvement. Incidentally, the records of the pathological department of the Johns Hopkins Hospital indicate that adrenal atrophy (and presumably adrenal insufficiency) is common in cases dying from status thymo-lymphaticus. Asthenia is a usual symptom and sometimes overshadows the other subjective symptoms, and, presumably, it is of adrenal origin. Such cases often suffer from severe metabolic disorders with an intoxication which is quite probably of endocrine origin.

Quite often the development of the bones is disturbed, the growth of the extremities being stunted and a condition of softening quite similar to osteomalacia has been attributed to thymus disorder. At least derangements of the calcium metabolism are quite usual in thymus disease.

The circulatory system is ineffective, due to hypoplastic changes in the heart and great vessels. As a result of these organic changes resistance to disease is low, "the constitution is poor" and trivial things may produce sudden death.

In young individuals the abdomen frequently assumes that type known as "pot belly" and there is important clinical connection between thymus disorder and rickets.

Thymic Asthma. The dyspnea of thymic origin has somewhat erroneously acquired the name "thymic asthma." This is really a form of inspiratory dyspnea due most usually to tracheostenosis caused by pressure of an enlarged thymus. It is only one of a series of symptoms of thymus hyperplasia and is not a distinct entity, nor is it amenable to treatment different from that which is directed at the removal of the thymus or, at least, the pressure that it exerts upon the structures adjacent to it.

SECTION IV. CHAPTER 10

DISTURBANCES OF THE PARATHYROID GLANDS

The parathyroid glands, sometimes called "the epithelial bodies," were discovered in 1880 but their significance was not hinted at until 1891 when Gley, of Paris, connected them with tetany. Since then much work has been done to establish the fact that the parathyroids are definite endocrine organs.

Parathyroid Physiology. The diagnosis of parathyroid dysfunction necessarily presupposes some information regarding their physiological effect upon the organism. Briefly, it may be said that while complete information about the parathyroid functions is not yet available, it is evident that parathyroids (1) exert a control upon calcium metabolism and (2) have an antitoxic action, the chief purpose of which is the destruction of "substances which have a predilection for influencing nervous tissue." The parathyroids are quite independent from the thyroid, both in origin, histology and function. This does not prevent a direct or indirect relation between the functions of the two systems. It is believed that parathyroid insufficiency, to some extent, checks the function of the thyroid.

Experimental removal of the parathyroids usually causes early death, preceded by a neuro-muscular symptom-complex described under the name of tetany, which is accompanied by a marked loss of calcium, a fact which has been emphasized clinically by the excellent results of MacCallum, of New York, and others from the administration of cal-

cium salts in the suppression of symptoms due to parathyroidectomy. An analysis of the cases reported indicates that the intensity of post-operative tetany in man is in inverse proportion to the amount of the parathyroid tissue that may be left.

The Symptomatology of Tetany. The principal symptoms of tetany, whether spontaneous or due to experimental parathyroid ablation, are very easily diagnosed. Intermittent tonic spasms of the voluntary muscles are the rule, especially in the extremities. The flexor groups of muscles are almost exclusively involved. Connected with these muscular symptoms are headache, asthenia, varying degrees of rigidity of the limbs, twitching and severe muscular pains. The contractions begin in the hands and later affect the feet, causing the muscles to become very hard to the touch and to oppose decided resistance to attempts to relax them. Fibrillary twitchings are sometimes seen. These experiences occur for varying lengths of time from a few minutes to several hours. Usually there are several attacks in the day. The patient is restless at night, and in severe cases, while consciousness is retained, extreme dyspnea may occur.

Several clinical tests are available, especially in the differentiation of mild and early tetany. The test suggested by Erb consists of the discovery of a marked irritability of the motor nerves, especially the ulnar, to galvanic stimuli. Very small amounts of electricity cause decided contractions, and this test should be made in all suspected parathyroid cases because of its sensitiveness and accuracy. Another common phenomenon, first noted by Trousseau, consists of the production of a tetanic spasm in a limb following compression of its main nerve trunks. Further, brief muscular twitchings in the face can be elicited in patients with tetany by gently tapping over the distribution of the facial nerve (Chvostek's Sign). All these tests, of course, are made between the spasms.

Another pathognomonic finding is a marked increase in guanidin and similar substances in the blood and urine, and it seems from the work of Noel Paton of Glasgow, Koch of Detroit, and others, that the conclusion is warranted that the parathyroids exert a destructive catabolic action upon guanidin and its precursors, for the presence of these substances and the results of their irritation of the body as a whole, and the nervous system especially, are very marked. The condition known as spasmophilia, an abnormal ten-

dency to convulsions in infants and children, is thought to be of similar origin and also associated with undue calcium depletion.

There is such a thing as chronic tetany, in which occasional paroxysmal tonic contractions of muscle groups are found, together with paresthesias (usually in the hands and feet), hyperexcitability of certain nerves and trophic changes in the teeth, hair, nails and bones.

A Hypoparathyroid Syndrome. Parathyroid insufficiency does not necessarily involve a picture of tetany such as has been given. Hertz, of London, reports a case of hypoparathyroidism where extreme depression, nervousness and restlessness appeared suddenly. The patient was continually on the move and slept very little. He was exceedingly tremulous, had difficulty in writing, and there was a continuous fibrillary twitching of the eyelids, but no tetany. The appearance was quite similar to Graves's disease, except that the eyes were sunken instead of prominent, and no thyroid could be felt. The appetite increased, and he ate enormously but lost weight. He had some difficulty in swallowing, due to irregular spasmodic contraction of the esophagus, and some intestinal pain, probably due to some similar cause. There was palpitation, the pulse was continually about 120, and his face and neck were deeply flushed. In this particular case, parathyroid therapy caused an entire cure, and it is proper to say that various other methods of treatment directed previously at a presumed hyperthyroidism were useless. This is a rare case, but serves to emphasize the parathyroid symptoms.

The condition of hyperparathyroidism does not seem to have been given consideration, though theoretically it should be possible; and at least one case is recorded in the literature.

Paralysis Agitans. It has been stated that various disorders associated with muscular tonicity and sympathetic irritability may be connected with the parathyroid glands, and the most thoroughly studied of these is Parkinson's disease, or paralysis agitans, in which it has been shown at autopsy that the parathyroids are quite commonly involved. Many clinical experiences with parathyroid feeding indicate a possibility of controlling the various well known manifestations of this disease. It is stated by Berkeley, of New York, that while parathyroid extract is not a "cure" for paralysis agitans, 60 to 70 per cent. of those who have given this remedy a fair trial for at least three to six

months have been greatly benefited,* and in such patients the progress of the disease has been arrested, or very materially retarded. Based upon the same reasoning, it has been thought that eclampsia was connected with parathyroid insufficiency, but this is not well established. Another point of clinical interest is a special sensitiveness to neurostimulant drugs, such as strychnia, which has been linked up with hypoparathyroidism.

To sum up, the parathyroids evidently are intermittently concerned in destroying certain wastes in the body, and their removal or insufficient function allows these products free play, with the resulting muscular and nervous irritation. It is well to add that certain digestive disturbances in children (gastric tetany) may cause a special toxemia which may result in dysfunction of these glands, and it has been noted that pregnancy puts an extra strain on the parathyroid functions, as evidenced by the occasional appearance of tetany in pregnant women and the common occurrence of tetany in partially parathyroidectomized pregnant animals. The chief clinical conclusion concerning the parathyroids is to connect them with conditions of marked neuro-muscular irritability.

SECTION IV. CHAPTER 11

PANCREATIC ENDOCRINE DYSFUNCTION

The pancreas is an organ with both an internal and an external secretion. It is conclusively established that the internal secretion is a product of the islets of Langerhans, while the external secretion is produced in the cells constituting the walls of the acinous portions of the gland. Without a doubt, these two functions are related to one another, and conditions likely to cause pancreatic indigestion are equally likely to cause pancreatic dyscrinism.

Quite the most important disease due to disturbed internal secretory function of the pancreas is diabetes mellitus,

* Berkeley gives parathyroid by mouth and hypodermically. Both are advisable for the first stage of the treatment; later, oral administration is advisable. I have developed a formula, No. 24, *Parathyroid Co. (Harrower)*, in which an average dose of parathyroid is supplemented by two known-to-synergize products, bile salts and spermin, the former to encourage hepatic activity and the latter to favor cell oxidation, two factors involved in this disease.

and the amount of work done upon various experimental aspects of this subject is literally enormous. There are actually hundreds of papers on the subject, in a dozen languages; the amount of experimental work upon pancreëctomized animals has been very great, and without taking much time or space, it may be said that the removal of the pancreas brings on immediate glycosuria, which may be mitigated or controlled by the successful implantation of pancreatic tissue and, quite often, by the administration of a pancreas preparation rich in its internal secretory product.

The Control of Sugar Mobilization. The pancreas produces a hormone, occasionally called the Langerhansian hormone, which von Noorden, of Frankfort, calls "the brake to the sugar factory." This has been called by Lepine, of Lyons, an anti-hormone, for indeed the chief function of the pancreatic internal secretion is not to "arouse or set in motion" but to regulate the mobilization of sugar, a function which is activated by the adrenal principle to which the pancreatic hormone is the direct antagonist. As a matter of fact, pancreatic diabetes, so-called, is in part at least a condition of adrenal sensitization due to the removal of part or all of the antagonizing hormone influences of the pancreas; and it is very probable that the initial disturbances of the digestive functions of this gland are responsible for the development of the diabetes, for diabetes is essentially a disease of those with overworked digestive organs.

In the experimental work upon various phases of the pancreas-diabetes question, it was discovered that the pancreas exerts quite a marked influence upon blood pressure, the general tendency being to reduce it, probably by its capacity to antagonize abnormal activity upon the part of the adrenal glands. The fact that the blood pressure is often very high in diabetes (pancreas insufficiency) tends to confirm this. It will be recalled that adrenin, the adrenal medullary principle, is a permanent factor in the maintenance of the normal blood pressure, and it is presumed that conditions of adrenal irritability or abnormal activity are likely to be associated with an increased arterial tension. This works out clinically very nicely, and it is a pleasure to be able to say that an organotherapeutic deduction has been made from these principles which is enabling us to reduce high blood pressure through the use of certain glandular combinations containing desiccated pancreatic substance. (See chapter entitled "Reducing High Blood Pressure," Sec. V, Chap. 15.)

The Pancreas and Immunity. Still another very important function of the pancreas concerns the resistance of the body to disease. Evidently, the pancreas exerts a well defined control over the immunizing powers of the body. Some years ago, I went into the study of the subject quite carefully and wrote a paper for *The Practitioner* (London), in which I showed that pancreatic dysfunction should be considered in every case of serious infection. Attention was called to the fact that in the experimental ablation of the pancreas for the purpose of causing artificial diabetes in dogs, the animals died from sepsis unless a small abdominal graft was made to maintain the pancreas endocrine control and thereby tide the dog over the serious operation, after which the graft could be removed later from the abdominal wall. Further than this, it is clinically well known that persons with diabetes are prone to aggravating infective conditions, as boils, carbuncles and gangrene. This may be an explanation for many favorable reports in regard to the use of pancreatic preparations in tuberculosis and other conditions where the resistance-maintaining department is overworked or incompetent.

So far as is known, there is no well defined condition of pancreatic hyperfunction, although such a condition may be physiologically associated with hyperpituitarism (acromegaly), in which it is known that there is a disturbance in the capacity of the organism to care for ingested sugars.

SECTION IV. CHAPTER 12

LABORATORY MEASURES IN DIAGNOSTIC ENDOCRINOLOGY

The majority of the measures which enable us to diagnose and understand endocrinopathies are largely based upon clinical observations rather than diagnostic tests, laboratory or otherwise. Yet, as we have developed our knowledge of the subject, various procedures of a laboratory nature have been mentioned as helpful and deserve consideration separately. The subject has been considered very fully by Rosenbloom, of Pittsburgh, in a series of papers published in the *Interstate Medical Journal* (1918, Nos. 10, 11 and 12), and a brief consideration of the most practical and useful of these tests, with a passing reference to

those which cannot well be made use of in ordinary clinical practice, will constitute this chapter.

Tests for Hyperthyroidism. One of the most constant results of hyperthyroidism is a condition of sympathetico-tonus (see also Sec. V, Chap. 4), in which it is found that there is a marked sensitiveness of the sympathetic and vasomotor nerve endings, so that very slight doses of the adrenal medullary principle are capable of causing a much more rapid and marked reaction than is usually the case. Several tests are based upon this phenomenon.

Loewi's Mydriasis Test. In his study of experimental diabetes in animals and later in diabetes mellitus, Loewi discovered that the installation of one or two drops of adrenalin chloride solution (1:1000) into the conjunctival sac will cause a pupillary dilation within half an hour, which reaches its maximum within an hour and lasts 10 to 18 hours. Associated with it is a marked diminution or total absence of convergence miosis, though the light reflex is preserved. This reaction is quite commonly found in pancreatic diabetes, and Loewi also suggested that this test might be helpful in latent hyperthyroidism on the basis that the hormones of the thyroid and adrenals are synergistic, both stimulating the sympathetic; hence in hyperthyroidism the sympathetic system would be in a state of increased irritability, and the dilator nerves to the iris (governed by the sympathetic) would respond abnormally to the introduced adrenalin. Quite a number have confirmed the value of this test, but some state that it is not invariably useful; at least, this test may be done as a routine with possible advantage, with practically no trouble, and without detriment.

Goetsch's Adrenalin Test. This test is also based upon the exaggerated sensitiveness to adrenal stimulation which results from thyroid irritability. Eight minims of 1:1000 solution of adrenalin are diluted with an equal quantity of sterile water and injected hypodermically into the arm. Immediately there is formed an area of blanching around the point of injection, and about the margin of this usually a red areola gradually shading off into the surrounding tissue. In about half an hour the center of the white area becomes bluish gray and lavender, and at the end of about one and a half to two hours the red areola takes on the bluish or lavender color, while that in the center disappears. This lavender areola remains for about four hours from the time of injection and is the most characteristic part of the test.

Accompanying the local reaction may be an increase in pulse rate with palpitation of the heart and a temporary exaggeration of the tremor and the nervous instability in general.

This adrenalin test has been used by Goetsch and Nicholson at Trudeau Sanatorium (*Amer. Rev. Tuberculosis*, Apr., 1919) in the differentiation of early tuberculosis from hyperthyroidism. If the patient, following the injections as indicated, reacts with manifest symptoms of hyperthyroidism, Goetsch believes that a positive diagnosis of this condition is justified and it will give a positive reaction whether associated with tuberculosis or not. On the other hand, tuberculosis uncomplicated by hyperthyroidism does not react positively to adrenalin, and they feel that in a considerable number of borderline cases showing symptoms more or less characteristic of both conditions, they can now pick out those with hyperthyroidism and treat them accordingly.

Calorimetry or Metabolimetry. Perhaps one of the most valuable aids to diagnosis is the calorimeter, the apparatus by which the basal metabolism is estimated. Basal metabolism is the minimal heat produced by an individual. By experimentation the average heat under fixed, given circumstances in healthy individuals is found by recourse to this instrument, and is expressed in calories per square meter of body surface.

Some use a tried equation made from the known height, weight, sex, and age, instead of the square surface area of the body, for the basis of this test. The measurement is made when the body is at muscular rest, but awake, 12 to 18 hours after the ingestion of food. Once the normal metabolic rate is fixed for an individual whose sex, height, weight, and age are taken into account, the calorimeter is used to measure the rate of his heat production (which coincides with the amount of oxygen he consumes), and the result is compared with the normal. The figures expressing the rate are plus or minus, according to the finding, and indicate the percentage above or below normal.

As with the common clinical thermometer, some diseases give a reading above normal and others below, so here the readings are marked plus or minus.

A Clinical Experience. A few months ago a young lady, about 20 years of age, who had recently entered my employ, asked for advice, knowing only that she had a slight enlargement of her neck and that she was more nervous than

formerly. I had her metabolic rate measured, and it was plus 74—an unusually high figure, by the way. Her pulse was 110-130 and temperature 99 degrees.

This extremely high B. M. R. could not exist if her trouble had been neurasthenia, the disease with clinical symptoms that sometimes simulate hyperthyroidism, for the basal metabolism is always near normal in neurasthenia. Therefore, considering the enlarged thyroid, the conclusion was quickly reached that she had true hyperthyroidism, and that her real trouble was hyperplastic or exophthalmic goitre, in this case the exophthalmæ not having yet developed, and the positive high percentage of findings showed that she was in a serious condition. She was ordered to bed without delay and local measures as well as suitable gland feeding were promptly ordered.

An additional advantage of being able to measure the basal metabolic rate is found during the time the patient is under treatment. If the rate is measured periodically, once or twice a month, there need be no uncertainty as to the rate of improvement and the prognosis.

Harrower's Thyroid Function Test. The administration of step-ladder doses of thyroid extract, accompanied by careful study of the pulse prior to, during, and for two or more days after the use of this extract may cause a material change in the pulse-rate, depending upon the apathy or sensitiveness of the thyroid. On the one hand, hyperthyroidism may be easily discovered by a lack of any reaction while, on the other hand, the pulse chart in hyperthyroidism is quite typical. (This subject is discussed more fully and explanatory clinical charts are reproduced in the chapter entitled "A Method of Testing Thyroid Function," Chapter 4 of this Section.)

The Respiratory Quotient. The increased metabolism of this disease can be measured by studying the products eliminated through the lungs by means of the clinical respiration apparatus of Benedict, or other similar apparatus, developed in the Nutrition Laboratory at Boston. This is a very complicated procedure, involving expensive apparatus, which enables one to determine the oxygen consumption, as well as the carbon dioxide production, both of which are considerably increased in hyperthyroidism.

Abderhalden's Ferment Test. Lampé and others believed that the blood serum of patients with hyperthyroidism contains ferments which are specific for thyroid tissue by following the Abderhalden method, and this indeed may be

true, but I have always felt that the technique of these sero-diagnostic tests was too complex for ordinary physicians, and even too much the subject of error in the hands of accomplished technicians.

Tests for Pituitary Dysfunction. Metabolism and the respiratory exchanges have been studied in hyperpituitarism, and in the somewhat rare uncomplicated cases there is no increase as in hyperthyroidism (q.v.), but unfortunately, it is not usual to have a pure pituitary monoglandular disturbance.

Marie's Artificial Glycosuria Test. The famous French neurologist, Pierre Marie, who first described acromegaly, also showed that it is often accompanied by disturbances in the sugar tolerance. Based upon this, it is possible to produce a "provocative alimentary glycosuria" by the administration of various forms of sugar, as follows:

1. *The Sucrose Test.* One hundred and fifty to 200 grams of cane sugar syrup are given to the subject in the morning while fasting. The urine is collected every hour and tested for reduction by means of Fehling's or Benedict's solution. A reduction makes the test positive.

2. *The Glucose Test.* The patient takes in the morning before breakfast, on an empty stomach, 150 grams of pure dextrin-free glucose dissolved in 300 c.c. of water. One can allow fifteen minutes in which to drink this solution. The urine is collected every hour for ten hours and each specimen tested for sugar. The patient stays on a milk diet during this time. The presence of glucose in the urine renders the test positive if it is known that the patient does not present a condition of spontaneous glycosuria.

3. *The Levulose Test.* One hundred grams of levulose are given in the morning on an empty stomach and the urine examined every two hours for the presence of sugar. A reduction shows presence of lessened ability to use this sugar.

4. *The Galactose Test.* Thirty grams of galactose are given to the patient in the morning on an empty stomach and the urine collected every two hours for six hours. The presence or absence of galactose in the urine is determined by Fehling's or Benedict's solution.

Sugar Tolerance Estimation. In hypopituitarism, there is a very marked increase in sugar tolerance; and while the above tests are carried out in the same manner, the patient with hypopituitarism is capable of tolerating very much larger quantities of the various sugars, and twice or

three times the amounts just indicated can be taken without a trace of glycosuria. (See Chapter 6, Section IV.)

Tests for Adrenal Function. *Adrenal Sensitization.* The most satisfactory laboratory test consists in the administration of one or two milligrams of adrenalin chloride (approximately 18 minims of the standard 1:1000 solution contain one milligram) by hypodermic injection. In cases of adrenal irritability, or hyperadrenia, a temporary increase in the blood sugar begins in about half an hour, as estimated by any one of the several methods now in use, and even the glycosuria may last two to six hours.

The Oculocardiac Reflex. In 1908, an Italian physician named Dignani called attention to a noticeable change in the pulse rate following compression of the eyeballs. This reflex has been found to be exaggerated in epileptics, and the reaction is more marked the more frequent the seizures. This reflex seems to be lost very early in tabes and may eventually be of differential diagnostic value. According to Peterson, of Copenhagen, this reflex deserves great attention from a medical, as well as a neurologic point of view, and is largely valuable in the study of paroxysmal tachycardia, a condition evidently due to disturbed *sympathetico-tonus,* a condition of sympathetic virility commonly connected with dysadrenia. According to Lian, of Paris, pressure on the eyeballs seems to be the most potent means at our command to influence the vagus and thus indirectly control heart action, and he recommends the use of this reflex test as a therapeutic means of arresting paroxysmal tachycardia.

Sergent's White Adrenal Line. Emile Sergent, of Paris, has described this vasomotor phenomena as a test of well-defined hypoadrenia. He traces a geometrical figure on the skin of the abdomen—a rectangle, triangle, or cross—obviating confusion with lines caused by folds of the skin, etc. The rounded end of a fountain pen is advised for the tracing. The figure should be made by a simple superficial stroking; one must not bear down or scratch the abdomen. After half a minute a pale line or band begins to be noticed following the tracing. Gradually this becomes more and more distinct and white, at the same time becoming larger, so that eventually the line exceeds in size the actual area touched by the pen. This white line attains its maximum clearness in the course of about one minute, and persists for one, two, or even three minutes before being gradually obliterated. This constitutes the reaction in well-de-

fined cases of adrenal insufficiency. Sergent considers his so-called *"ligne blanche surrénale"* as due to the hypotension brought about by the hypoadrenia. It is known that in arterial hypotension there is present a peripheral vasodilation produced by a slight stimulation of the skin. Vasoconstriction replaces the vasodilatation with the resulting white line.

Tests for Parathyroid Dysfunction. *Erb's Test.* The laboratory test for hypoparathyroidism, or tetany, suggested by Erb is probably the most dependable and uniform of all the clinical procedures in the study of this condition. Galvanic stimuli of the motor nerves, especially the ulnar nerve, which in ordinary individuals are inactive, cause decided contractions in tetany. A kathodal opening contraction below five milliamperes is particularly significant and comparisons with normal individuals show that in tetany contracture follows exceedingly mild stimuli.

Tests for Pancreatic Insufficiency (Endocrine). The internal secretory function of the pancreas is well known to antagonize that of the adrenals and at the same time is intimately concerned in the metabolism of carbohydrates. Deficient pancreatic secretion is accompanied by glycosuria; hence the administration of sugar will aggravate this. This does not differentiate between hepatic and pancreatic insufficiency, but in the former instance, the administration of desiccated pancreas substance may aggravate the glycosuria, while the use of desiccated liver substance for a week or more would cause a considerable reduction in the elimination of sugar in the case that the hepatic element was not prominent.

The Cammidge Test ordinarily is considered to be a useful measure for discovering whether the balance between the pancreatic and adrenal secretion is disturbed and to what degree. It is a complicated laboratory procedure, the discussion of which is unwarranted here.

Loewi's Test for Pancreatic Diabetes. The test suggested by Loewi as a means of discovering pancreatic insufficiency in diabetes is identical with that already mentioned under the heading "hyperthyroidism" and consists of instilling one or two drops of adrenalin chloride solution into one eye. Garrod, of London, has found this test positive in all pancreatic cases but rarely in other cases. Murray, of Manchester, agrees with him but does not believe it is as useful in hyperthyroidism as in diabetes. In this instance, it is presumed that the dilation occurs because of the mutual

stimulation of the sympathetic by the thyroid and adrenals, and since the pancreas definitely antagonizes the adrenals in normal physiology, the removal of this antagonism would naturally tend to an adrenal or sympathetic irritability and hence of the dilator fibers of the iris.

Clinical Test with Adrenalin. Individuals with pancreatic diabetes are unusually sensitive to adrenalin. It has been noted time and again that the use of adrenalin in nose and throat surgery in diabetics, for instance, causes a marked increase in the average sugar output; and while such experiences amount to a "therapeutic test," it is not advisable to administer adrenalin products when the adrenals already are so thoroughly uncontrolled by the absence of the normal antagonism of the pancreas "antihormone."

The Thymus Gland. *Differential Blood Count.* The study of the relative leucocyte counts in individuals with a persistent thymus usually shows a lymphocytosis, the small lymphocytes being increased very markedly. Of course, there may be other causes for lymphocytosis—tuberculosis, for example—but this serves as one small factor in building up the picture.

Fluoroscopy. A persistent thymus often may be seen with the fluoroscopic screen. There is an increased shadow in the area represented by the triangle, the base of which is just below the suprasternal notch and the apex of which reaches to the level of the aortic arch or approximately the junctions of the second and third ribs with the sternum. Often the shadow is especially noticeable on either side of the angles formed by the clavicles, sternum and upper ribs.

SECTION V.

EVERY-DAY ORGANOTHERAPY

The following chapters have been developed from correspondence, lectures and articles on the practical every-day problems of the average physician. The one idea running through them all is to emphasize the immense possibilities of organotherapy in routine practice. I believe I have shown that there is an endocrine side—and an important one—to many troubles not ordinarily connected with the ductless glands. The opportunities to attain better results in general practice have been materially broadened by the application of some of these ideas gathered from many scattered sources, worked out in The Harrower Laboratory and then tested in "the crucible of the clinic" by literally thousands of my colleagues.

SECTION V. CHAPTER I

ASTHENIA: THE COMMONEST SYMPTOM IN MEDICINE

Practically all individuals with overburdened systems, that is to say, the majority of the cases of chronic diseases which are so very common, suffer from *asthenia*—loss of strength. In fact, asthenia is probably the commonest single symptom seen in medical practice. The so-called "fatigue syndrome"—in which the patient tires too easily and too early, in which not only is there muscular tiredness, but initiative is lost and mental capacity is dulled—is one of the most important manifestations in chronic toxemias.

Cellular Intoxication. As a matter of fact, asthenia is really another name for cellular intoxication—the muscles after work are tired because of the excess of intracellular wastes which have been produced in a quantity sufficient to overburden the usual means of elimination as well as all other mechanisms that are influenced by such toxins. Of course, the treatment is rest or refraining from all work and activity, during which time the poisons ordinarily are

carried away by the circulation and disposed of. Muscular asthenia may be due to an increased production of these toxins or reduced capacity to carry them off as manufactured. Both causes are commonly associated, and the latter probably is the more important.

A Toxic Vicious Circle. If the circulation is insufficient, i. e., if the blood-pressure is low and the "circulatory pep" is below par or, in other words, if the regulating mechanism which controls circulation, cardiac efficiency and blood-pressure, is not efficient, asthenia must result from the accumulation of the ordinary amounts of cellular wastes. This would be aggravated if in addition to this there were an augmented production of these products. It also happens that poor circulation causes poor oxidation, which in turn causes an accumulation of intracellular wastes. So we have a vicious circle, the one condition aggravating the other and *vice versa.*

The tendency of the cell is to die. "Man begins to die as soon as he is born." This means that if the perpetual production of wastes is modified ever so slightly or the efficiency of the emunctories fails, there is going to be trouble. *And the initial manifestation of this kind of trouble is asthenia.*

What is the earliest symptom of incipient tuberculosis? Asthenia. What is the chief sign of the other most common toxemia—intestinal stasis and alimentary intoxication? Asthenia. What is the commonest factor in any infection, focal or otherwise, or infectious disease? Asthenia.

Adrenal Insufficiency. What underlies the asthenic syndrome? We have already said that toxemia, intracellular or extracellular, is the commonest cause; but how does it bring it about? In the answer to this question lies the basis of a new conception of disease, and a new, or at least an ignored, method of treatment. *The chief cause of asthenia is insufficiency of the adrenal glands.* Hypoadrenia is probably the most common endocrine dysfunction. It deserves consideration wherever there is asthenia, no matter whether it is called neurasthenia, psychasthenia, myasthenia, chemasthenia, cardiasthenia, "neurocirculatory asthenia," or any of the numerous other names given to various clinical manifestations of the one fundamental underlying trouble.

"Why do you connect the adrenal glands with the asthenias?" This question has been put to me a hundred times or more. Here is the answer as concisely as I can give it: The adrenal glands produce an internal secretion which is known to exert an amazing influence upon the circulation.

Adrenin, as this hormone is called, is a predominant factor in the maintenance of cellular tone and especially that of the unstriped muscles of the heart and intestines; it keeps the blood-pressure up; it thus favors both oxidation and detoxication (and it has been shown that adrenin also has a direct influence upon oxidation besides its indirect effect through its control of circulatory efficiency); by its musculo-tonic effect, digestion and alimentary tone are maintained, hence hypoadrenia favors a condition of atonicity of the alimentary musculature which, in turn, causes stasis and further toxemia—another of the dread vicious circles. This hormone, adrenin, has been shown to "control the sympathetic system," thereby bringing about the conditions just mentioned as well as other subtle chemical regulations which need not be mentioned in this brief article.

The Sensitiveness of the Adrenals. Poisons of any kind, in the most minute dosage, have an immediate effect on these most sensitive of all the organs of the body. It is the business of the adrenals to respond to these influences, for if they do not, the increased circulation and augmented oxidation, which become essential and which are brought about automatically as the body's greatest means of protection against disease, fail to take care of the toxemia. It is true that there are innumerable forms of toxemia, some toxins which are the usual wastes of the body cells—some which are unusual, as the products of intestinal putrefaction, some which we ingest wilfully (as coffee) or accidentally, some which are produced by the aberrant activity of certain organs and especially the endocrine glands (for "too much of a good thing is a bad thing"), and, finally, some poisons which are automatically made in the subtle chemical changes which occur in shock, emotional storm or the various mental states like fear, rage, worry, and so forth. In other words, practically all forms of stimuli of the nature mentioned stimulate the adrenals. Too often the persistence of these stimuli is more than these little glands can bear, and they play out. We have as a result a functional hypoadrenia, *and the first symptom is asthenia.*

It should be unnecessary to give clinical proof; it is so extremely common. We have already mentioned the asthenia of the earliest stages of tuberculosis, before the cough and sputum materialize. We know that "post-influenzal asthenia" is indeed a most uniform result of the toxemia of this scourge. During the influenza epidemics the unusually severe toxemia resulted in serious depletion of the

adrenals in many thousands of cases, and brought attention very forcibly to the importance of these glands as maintainers of the tonicity of the body. Not merely influenza, but all acute infectious diseases and the accompanying toxemias, as well as all chronic foci of infection, are common factors in overstimulating the adrenal glands. *If these little glands were not stimulated, the body's defenses against these conditions would not be initiated properly, and death* would ensue. We know that following pneumonia, typhoid, malaria or any acute, infectious disease, hypoadrenia is the rule. We know that an emotional shock—bad news, an accident, an unusual and strenuous mental impression as seeing an accident or death—will cause a "let-down" that is nothing but a more or less serious manifestation of adrenal asthenia. In some unusually susceptible individuals—those, for instance, whose adrenals have had much to put up with—far less important stimuli, as an unexpected noise or slight "tiff" at home, cause an asthenia that is as well defined as it is usual.

"Endocrinasthenia." From a clinical standpoint, it is impossible to have a combination of conditions such as the various asthenias already mentioned without **endocrinasthenia**—the natural result of functional insufficiency of the glands of internal secretion, or hypocrinism. The adrenals are too intimate with the other endocrine glands to be affected alone. In fact, not only is this endocrinasthenia a very real clinical entity, but it is the underlying cause of the other asthenias, for it is impossible for an individual to be "all run down" and to be suffering from asthenia without both the cause and the effect exerting their influence upon the sensitive endocrine organs. In other words, when the body is tired the endocrine glands are also tired. When the circulation is slowed the endocrine glands are affected with the rest of the body, and when the vital service of hormone production by the endocrine system is reduced ever so little, we have asthenia as one of the immediate results, whether the toxemia is a prominent factor or not, and the greater this endocrinasthenia the worse do the other forms of asthenia become. We have another serious vicious circle.

The big thing about functional hypoadrenia is the possibility of modifying its effects by supporting the endocrine glands. Thousands of run-down, tired-out, asthenic individuals—many of them labeled "neurasthenics," many called "convalescents," many in whom the asthenia is ignored because it is submerged by some more obvious con-

dition, as rheumatism, ovarian dysfunction, a focal infection or some mechanical difficulty in the abdomen—have as their most prominent and their most responsive symptom asthenia, resulting from a plain case of adrenal insufficiency.

The Symptoms of Adrenal Insufficiency. What are the usual symptoms besides asthenia? Fatigue is the principal result, and it may be of a most severe character. The patients are tired out and unable to accomplish the usual mental or physical work. They have *an aggravated degree of muscular fatigue* which extends to the involuntary muscles, causing heart weakness (very commonly these cases are classed as "myocarditis" when in reality there is no real structural change in the heart muscle at the time), the vessel walls lose their tonicity, and as a result there is a condition of *low blood-pressure* which, in turn, causes *cold hands and feet* and other evidences of circulatory insufficiency.

The muscles of the alimentary canal are equally atonic, and as a result there is *constipation,* indigestion and the well-known *intestinal stasis* and, naturally, malnutrition, loss of weight, anemia, and so on. Parenthetically it may be stated that the toxemia from intestinal stasis is just as much a cause of adrenal stimulation as that which results from any other poisoning, and consequently the adrenals are still further depleted, with still more atonicity. Thus a vicious circle is produced.

In fact, the Addisonian syndrome which results from severe organic adrenal disease is merely an incurable, aggravated form of the very same trouble, the difference being merely one of degree. Does this fit in with several cases on your list now? Yes, indeed. Then why not support the adrenals, in addition to prescribing elimination, rest and other measures to remove underlying causative elements? Adrenal support is a great advance in every-day practice. It works; and the results are sometimes wonderful. It may be given practical application with the greatest facility by prescribing *Adreno-Spermin Co.* (*Harrower*), a plurigland-ular formula which I devised, and which combines adrenal support from a suitable dose of adrenal substance plus "the dynamogenic hormone" spermin (from the interstitial cells of Leydig in the testes), phosphorus in the form of calcium glycerophosphate, supplemented by a very small dose of thyroid extract.

The obvious and rational measures for the treatment of all forms of asthenia are (a) rest, (b) the removal of as

many as possible of the aggravating factors such as toxins, both those produced in the body (alimentary) and those taken into the body, wittingly or unwittingly; and circumstances calculated to stimulate emotional elements, like worry, fear, pain, etc.; (c) the natural stimulation of the dynamogenic factors in the body, e. g., the glands of internal secretion, by means of organotherapy (on the well-known principle of homostimulation represented in the Adreno-Spermin formula just referred to); and (d), finally, suitable nutrition, both as regards food, water, and especially the mineral elements of the organism. All of these physiological measures should be recommended simultaneously; and many hundreds of experiences with this procedure, more especially when "adrenal support" is given as suggested, convince one that this endocrine encouragement "increases the pep" or, in other words, antagonizes asthenia. In this connection, it may be remarked that in addition to bringing about a noticeable change in the tendency to muscular fatigability or tiredness, it is possible to get a very fair idea of the benefit *in figures,* for such treatment increases the lowered systolic blood pressure, increases the subnormal temperature and increases the elimination of urinary wastes, especially urea.

The Essentials of Adrenal Support. The matter of giving consideration to the adrenal or endocrine factor in asthenia is important in the extreme, and if organotherapy is rational in Addison's disease it is doubly so in these functional conditions since they are far more likely to respond to this physiological support. For convenience some of the essential facts are arranged below in semi-tabular form so that they may be the more readily appreciated and applied:

PHYSIOLOGY. The Adrenal Hormone (adrenin)

(1) Regulates the sympathetic system;
(2) Maintains muscular tone;
(3) Supports cardiac action;
(4) Keeps the blood pressure up;
(5) Facilitates oxidation, and thus
(6) Antagonizes fatigue.

Adrenal Function is deranged by

(1) Toxemia (acute and chronic)
Food poisons and drugs; intestinal stasis; focal infections; infectious diseases.
(2) Emotional Stimuli
Fear and worry; pain; shock.

(3) Dyshormonism

Such as ovarian disease, thyroidism, etc.

The adrenals coöperate with the other endocrine glands, especially the thyroid and gonads.

DIAGNOSIS. Adrenal Depletion (hypoadrenia) may be diagnosed by noting two or more of the following:

(1) Asthenia, "the fatigue syndrome," with muscular and psychic inefficiency or "lack of pep;"

(2) Hypotension with cardiasthenia, cold extremities and internal venous stasis—the so-called "hypo-sphyxia" of Martinet;

(3) Hypothermia—Subnormal temperature;

(4) Malnutrition due to the poor oxidation and elimination;

(5) Acidosis in greater or less degree is also naturally present.

THERAPEUTICS. Adrenal support by suitable organo-therapy properly should accompany detoxicative and hygienic measures.

Adrenal Substance homostimulates the adrenals and replaces, in part, the deficient adrenin.

Spermin from the Leydig cells of the gonads stimulates muscular tone (dynamogenic) and cell chemistry.

Thyroid Extract encourages endocrine action generally, and in hypoadrenia there is always hypothyroidism.

Calcium Glycerophosphate is not only a useful mineral but is considered to have an especially beneficial effect in neurasthenic conditions.

The above are suitably combined in an effective pluriglandular formula, *Adreno-Spermin Co.* (*Harrower*), which supports the adrenals, antagonizes asthenia and raises lowered blood-pressure.

SECTION V. CHAPTER 2

ADRENAL SUPPORT IN TUBERCULOSIS

In a recent issue of *The Organotherapeutic Review* a correspondent, the Superintendent of a sanatorium in Indiana, wrote the query department as follows: "I would be very pleased to receive your suggestions for the use of organo-

therapy in tuberculosis. The asthma, the low blood-pressure, the chronic continuous poisoning, the low Arneth blood count surely indicate a condition needing special boosting and more than we have been in the habit of giving."

The syndrome mentioned by this writer is, to my mind, essentially of endocrine origin. Practically every one of the symptoms enumerated is related to disturbed adrenal function; and I believe that the adrenal element in the tuberculous is as early, constant and important as any other factor, whether cause or effect. Perhaps the truth of this statement can be verified best by testing in "the crucible of the clinic." Clinical results are the only factors that count for very much in medicine. We can theorize all day, but this does not cure our patient. It may be all right to theorize; but it is far more practical and helpful to establish the reasonableness of some suggestion that may be new to us than to pass it up without thought.

A great many items have been published, especially in French, on the advantages of various organotherapeutic procedures in tuberculosis. Some of them are sound; some are questionable. We still have the tuberculosis, and all these statements have not controlled this plague. I am not pessimistic, however, for some of these reports are really "getting us somewhere," especially the splendid contributions of Emile Sergent, of Paris, whose original interest in *"l'insuffisance surrénale"*—hypoadrenia—centered in his studies of the tuberculous, and from which has been developed much of real value in endocrinology. Sergent is an accepted authority; he has proved his points. His "Collected Papers on Adrenal Disorders—1898-1920" is a wonderful book, though it is in French, of course. Suffice it to say that Sergent has shown us that *adrenal insufficiency is the rule in many cases of tuberculosis.* In fact, the first suspicious manifestations of tuberculosis are of adrenal origin, for asthenia or "the tiredness of incipient phthisis" is the essential initial symptom, to be followed shortly by the subnormal morning temperature—and all this before there may be any cough or sputum.

Sergent's Views. I have translated several paragraphs from the above book, and submit them here in support of my own attitude:

"Adrenal opotherapy finds its principal usefulness in the course of tuberculosis in three conditions. It is well known that the signs of adrenal insufficiency are by no means rare in tuberculosis, and, of course, these are the first indications

for organotherapy; but one ought to have special recourse to this method when the cardiotonic and vasoconstrictor influence is desirable. In this connection I will show you that it constitutes an excellent adjuvant to the treatment known as remineralization.

"Your attention has already been called to the Addisonian syndrome and also to the usual syndromes of typical adrenal insufficiency, or the *formes frustes* of Addison's disease. In these cases the patients show predominating lesions in their adrenal glands, and the clinical picture which develops, is a typical one. We will not now occupy ourselves with these well-defined cases. I wish to describe to you those cases in which attention is directed away from the actual pulmonary lesions, but in whom, however, the careful examination reveals signs of an insufficient functioning of the adrenal glands with or without changes in the skin in the nature of melanoderma.

"The adrenal glands of these individuals do not present at autopsy characteristic lesions of tuberculosis, but they are altered, nevertheless. Babès has found sclerosis and cellular alterations quite commonly. Lucien and Parisot have emphasized the frequent diminution of physiologic activity of the adrenals in the tuberculous. Boinet has described a condition in advanced cases, under the term 'Addisonism,' a combination of clinical symptoms, indicating a certain degree of adrenal insufficiency. Laffitte and Moncany have reported similar facts and have used the term *'petite insuffisance surrénale,'* or minor hypoadrenia. Sézary has found a sclerotic adrenal condition in many tuberculous persons in whom marked loss of weight and extreme muscular atrophy were contrasted with the slight extent of the actual pulmonary lesions. I have myself observed and published many analogous cases which I have classed in two categories: Those positively tuberculous individuals, who are tired rather than weak, with low tension, in whom one can discover a number of discrete pigmentary areas on the skin and on the mucosa of the mouth. The others, on the contrary, who do not show the slightest degree of pigmentation, but in whom the extreme asthenia and loss of weight are striking. If you examine them more carefully you will see that this nutritional change is not solely due to a disappearance of fat, but that there is also a considerable loss in muscular tissue. Auscultation develops signs of a quite well localized tuberculous process, and in no case is it comparable to the real gravity of the

general condition. One hates to conclude, under such circumstances, that there is a special form of tuberculous infection of a hypertoxic character, *and is really led to believe that the accompanying adrenal insufficiency may be the cause.*

"You will find also a large diagnostic element in the results of organotherapy. I have observed a certain number of individuals in whom I have, in this fashion, proved absolutely the adrenal origin of these findings. These facts have a very great practical importance because you can, if you care to, institute a useful therapeusis. You will not use adrenalin, but the total extract of the adrenal gland. I have been in the habit of using ordinary relatively small doses representing perhaps thirty centigrams of the desiccated powder. If this produces neither vertigo nor headache, I rapidly increase the dose to sixty or even ninety centigrams a day. This intensive medication ought not to be continued for a long time. It is preferable to push the dose for eight or ten days, separated by intervals of an equal length.

"Of course our investigations should not be limited to these matters. You should always study the arterial tension and will know when to stop if you cause a relatively too rapid increase in the tension. You will push the treatment, on the contrary, if the tension falls. You will often be very pleased to find that a low tension has been increased very decidedly and to see a progressive attenuation of the usual symptomatology of general adrenal insufficiency, and particularly the asthenia and malnutrition.

"Do I believe that this has a direct action upon the tuberculosis itself? Evidently it does not; at least, not directly, but in raising the general response of the individual and in putting him into a better general state, you are favoring the fight and raising the efficacy of the body's powers of controlling the actual tuberculous infection. The good effects of this practical method have been confirmed by Rénon, Gourand, Paillard and Lereboullet. It goes without saying that the usual routine treatment of tuberculosis ought to be instituted at the same time as the adrenal support."

Adrenal Insufficiency Predisposes to Tuberculosis. It cannot be denied that every person with tuberculosis, whether of the lungs or elsewhere, irrespective of the stage of the infection, has a pair of unduly burdened adrenal glands which are expected to regulate many vital sympathetic

functions and which are subject to the baneful influence of those very disorders of metabolism which predispose to the infection. Poor oxidation, malelimination, bad nutrition affect the adrenals before the invasion of the bacilli. The adrenal factor discussed in the previous chapter almost invariably antedates the actual infective process. Did you ever think how common a predisposing cause to tuberculosis is a cold, la grippe or the "flu?" Have you found out that hypoadrenia is quite the biggest factor in influenza, pneumonia or even a bad cold? That it is due to the bacterial and other toxemia and is the reason for the uniformly low arterial tension, the severe asthenia and the invariable hyposphyxia? And, by the way, this circulatory syndrome described by Prof. Alfred Martinet is extremely common in tuberculosis. "Hyposphyxia" is a condition of poor circulation, with cold extremities, internal venous stasis (abdominal and pulmonary), cardiac weakness *and hypotension.* These individuals are suffering from hypoadrenia; the adrenals are supposed to maintain circulatory and cardiac tone, and, being depleted, the circulatory cause of tuberculosis obtains.

Speaking of the involvement of the adrenal functions in influenza, pneumonia and other acute infectious diseases, and my view that adrenal support was in order as a part of the treatment, I laid down in the February (1919) issue of the *Review* the following points:

1. The blood pressure is low following influenza.
2. The severe asthenia or "let-down" which characterizes this disease, and especially convalescence from it, is a part of a syndrome so nearly identified with hypoadrenia that it is not unfair to call it by that name.
3. The circulatory insufficiency that accompanies influenza—the hypotension, subnormal temperature, venous stasis and cardiac asthenia or "hyposphyxia" (Martinet)—is the chief predisposing cause of the serious and all-too-common sequel, pneumonia. (Poor circulatory efficiency with stasis certainly does not favor resistance to the pneumococci or any other germs.)
4. Attempts to make these facts of service establish as fully as sphygmomanometry the rationale of this conception. *In other words, the success which follows adrenal support emphasizes the importance of the adrenal depletion.*

Why should not adrenal support be rational in tuberculosis as it has been proved time and again in influenza? It is, and the raised blood-pressure is not the only obvious

benefit, either. There is a production of "pep" quite similar to that we have found from strychnia or other time-worn tonics, but it just happened that this fatigue-antagonism is not due to stimulation but to a more nearly normal physiology (on the part of the adrenal system) resulting from the homostimulation (referred to in Section II), which means better circulation, better oxidation and a diminution of causes rather that effects. Is not this logical?

The Toxic Element in Tuberculosis. Again consider the matter from another standpoint. It is certain that every sufferer from tuberculosis is toxic; not merely from focal poisoning, but from alimentary intoxication. The toxemia antedates the infection; and when the infection has become obvious the toxemia is so much greater. Toxemia is the greatest single cause of adrenal stimulation. It must be thus, for it is a large part of the functions of these little glands to react to the slightest poisoning—irrespective of its origin—so that the circulatory and detoxicating mechanism which they control may be stimulated in order to control of toxemia and its effects. Overstimulation produces hyperadrenia, the most usual findings of which are sympathetic irritability, dry mouth and throat, and the occasional "digestive crises" which come on without apparent cause and pass off very soon. It should be stated here that a condition of well-defined hyperadrenia is rare, merely because the adrenal principle—adrenin—is oxidized with unusual ease and rapidity (that is why adrenalin therapy is less efficacious in prolonged hypoadrenias) and, too, because the adrenals cannot stand prolonged overstimulation, and become depleted—knocked out!

So adrenal insufficiency is indeed common in tuberculosis. In my estimation there never was a case in which the adrenals were not involved, though I do not want it understood that I am referring to actual cellular pathology or adrenal tuberculosis. I repeat: *Tuberculosis is a disease in which the adrenal functions are seriously impaired.* The chronic continuous poisoning referred to by this correspondent is exerting its inexorable influence upon the adrenals with the result that muscular fatigue is the rule, oxidation is below par (study the urinary solids and be surprised at the uniformly poor elimination), the temperature is subnormal at times, the blood pressure is 110 or less—very ordinarily less, depending upon the length of time that the adrenals have had to stand the toxemic hammering—and the patient is "all run down." The syndrome of hypoadrenia is com-

plete. We have a "functional Addison's disease," which may and occasionally does develop into the real Addisonian syndrome, which consists of the aforementioned symptoms in an aggravated degree, as well as the typical pigmentation and Sergent's "white adrenal line."

The Rationale of Adrenal Support. Now if this sounds sensible, why should we not, in addition to our other efforts in the line of hygiene or medication, attempt to support the overworked adrenals? Candidly, I do not believe that adrenal support will make any direct and material difference to the extent of the infection, nor that it will reduce the virulence of the invading organisms, whether the *B. tuberculosis* or the invariably associated pyogenic cocci. But I most assuredly believe in adrenal support, whether as a part of the treatment of tuberculosis or any other condition in which the adrenals are depleted. If some of my colleagues would only get the idea that I do not believe in organotherapy as the treatment of this, that, or any other disease, and that the study of endocrine function is or should be a *part* of the complete study of a given case, they would be less liable to mislead themselves—and others.

Is tuberculin a good thing? Most of us will say "Yes." Shall we ignore it, then? No; we will judiciously add it to other indicated measures. Why not the same attitude to the important subject under discussion? One remedy or procedure may be ever so good, but it does not necessarily follow that it is, therefore, *the* treatment. We will continue to use suitable diet and hygiene, tuberculin may help a lot, so will proper intestinal antisepsis (I am convinced that benefit from guaiacol, thiocol, calcreose or other similar remedies is more decidedly alimentary than pulmonary) and to all this add a careful consideration of the adrenal functions. If they are really depleted and the patient shows the usual syndrome already mentioned, let us encourage adrenal physiology by homostimulative organotherapy in the same way we have been doing this for years in other conditions of hypoadrenia. This fits in splendidly with our other measures in the treatment of tuberculosis *and supplements it*—let me emphasize—not supplants it!

I have hesitated to say very much in my literature about my formula, *Adreno-Spermin Co.* (*Harrower*), in tuberculosis, because I felt that I would be promptly misunderstood and branded as attempting to capitalize the attitude common to the tuberculous and to many of their medical advisers and be criticized for boosting this formula as a

remedy for this particular disease. It is not; but it tends to raise a lowered blood-pressure—by actual sphygmomanometry, it increases oxidation—by the urinary findings, it certainly favors the cellular chemistry, and hence nutrition, and does so by supporting the adrenals. And if the adrenals are depleted, no matter whether the name of the accompanying disease is Addison's disease, neurasthenia, post-influenzal asthenia, tuberculosis or whatnot, to support them and favor the betterment of their all-important functions is a sound therapeutic procedure.

Possible By-Effects. A point has come up a number of times in regard to possible by-effects of this method. For instance, one physician inquires: "Do you feel that it is safe to give the *Adreno-Spermin Co.* to a patient with advanced tuberculosis who has previously had hemorrhages but whose pulmonary condition has been quiescent for a year, the blood pressure being within the normal limits? Would you expect this preparation to give relief from the neuro-muscular asthenia in this case? Do you consider that tuberculosis *per se* is a contraindication to any one of the glandular products?"

The Adreno-Spermin formula is active for three reasons: It supports adrenal function and thereby raises sympathetic tone, including abnormally low blood-pressure, etc. It has a dynamic effect, especially on muscle, due to both the adrenal content and the spermin, which is believed to be the best musculo-tonic remedy of its kind. It contains neuro-tonic elements (lecithin and a generous dose of glycerophosphate of calcium) and hence has some effect upon nutrition, especially where the accepted cellular influence of phosphorus is likely to be helpful.

I do not believe that the adrenal stimulation brought about by the small and gradually active doses of adrenal substance would favor hemorrhage in a case such as is mentioned, though pituitrin or adrenalin injections might be contraindicated for their decided and temporary pressor influence. The Adreno-Spermin formula has no immediate or active effect—it is very gradual in its action and therefore less likely to have contraindications. Remember that organotherapy is really a form of endocrine education. The homostimulant effects of gland extracts favor the reëstablishment of normal endocrine function in the glands which correspond to those from which the extracts are made. This explains a large part of the benefits obtainable from organotherapy.

Such treatment supports the adrenals and gradually raises an abnormally low tension; but in a normal individual it makes little or no difference to the average blood-pressure.

Tuberculosis is not a contraindication to organotherapy. In fact, with the exceptions just mentioned—the rapidly acting pressor principles—organotherapy may help much as has been suggested. Again, if a tuberculous girl has an ovarian dystrophy, to mitigate it by suitable organotherapy surely is proper; just as an individual with hepato-biliary insufficiency who happens to have tuberculosis will benefit from suitable hepato-biliary stimulation as with the use of *Hepato-Splenic Co.* (*Harrower*), which, by the way, seems to have a good effect on malnutrition with alimentary laziness and has been used with benefit in many cases of tuberculosis in which the digestive element was prominent.

The subject is a large one, requiring more space than can be given to it here. The great point to remember is this: If adrenal function is depleted *and ignored,* our best therapeutic efforts will be less effective because of the extreme importance to resistance of the circulatory, sympathetic and metabolic function maintained by these glands. The tuberculous individual has a hard enough fight—any assistance that we can render is worth while, especially when it is so necessary, so generally overlooked, and so comparatively easily accomplished by means of a suitable organotherapeutic support *added to the other indicated treatment.*

SECTION V. CHAPTER 3

THE THYROID FACTOR IN TUBERCULOSIS

That there are other endocrine aspects to tuberculosis is not denied. We have seen in the previous chapter that many clinical facts make out a good case for an adrenal aspect to this common infection. Now I purpose to reprint a communication of my own, published in *American Medicine* (December, 1920), which explains some things regarding the thyroid aspect of this disease:

"Because of my special interest in endocrinology, and because I live in sunny Southern California, I am frequently confronted with problems which connect the glands of internal secretion with tuberculosis. It has occurred to me to

set down a few ideas on this subject as I judge from a number of comments that the medical profession as a whole may not be as appreciative of the importance of the endocrine aspect of tuberculosis as it deserves.

"As is well known, the thyroid gland is a very important factor in the control of the defences of the body. Aside from being the most important regulator of the chemistry of the cell, it is also proved by Sajous and others to be a factor in the immunity response of the body to infections. Consequently any condition as definitely a toxemia and an infection as tuberculosis is known to be, necessarily must influence the thyroid gland, and through it also those functions over which it presides.

"Let us first consider for a moment the influence of toxemia. The thyroid gland is probably the greatest single factor in the detoxicating mechanism of the body. It is also equally concerned in the stimulation of the other features of the cell chemistry. In other words, intracellular oxidization depends upon the thyroid hormone. If toxemia lays an extra burden upon the thyroid, one would expect to find a well defined thyroid aspect in tuberculosis, *and we do very routinely.* Both thyroid irritability, and hypothyroidism, may result from the conditions which, combined, we call 'tuberculosis.' You note that I refer to 'conditions' rather than to a single entry, for tuberculosis is never a single problem. It always involves a number of factors among which the actual infection by the tubercle bacillus is really but a small part. As a matter of fact, the associated pus germs usually produce a greater degree of toxemia and endocrine disturbance than the actual *B. tuberculosis* itself, and all students of the subject admit that a pure tuberculosis infection is a rare thing.

"No matter whether the trouble is purely tuberculosis or whether it is a mixed infection, the thyroid gland is bound to be influenced, not merely by the bacterial products themselves, but by those other wastes which result from the symptom-complex which is associated with the infection. I am referring particularly to the asthenic condition which is pathognomonic of tuberculosis, a condition which, by the way, involves the adrenal glands very definitely and to which I have referred previously in other communications, and which makes serious changes in the cellular chemistry.

"If the thyroid mechanism of an individual is in good order the stimulation from these toxins associated with tuberculosis causes thyroid irritability, as a result of

which there are well defined symptoms akin to hyperthyroidism. In fact, hyperthyroidism occasionally has been found as a part of the syndrome of tuberculosis, and Emil Goetsch has called particular attention to the value of his method of differentiating true hyperthyroidism and the quite similar condition which is associated more definitely with tuberculosis. I do not believe, however, when the symptoms which simulate hyperthyroidism are found in tuberculosis that they are due to anything else than an irritation of the endocrine glands as a whole, and the thyroid and adrenal glands together in particular.

"If the stimuli to thyroid are not sudden and severe, *i. e.*, if they are of a long-standing, persistent, nagging variety, there is not so likely to be the strenuous reaction of the thyroid to these influences and in course of time the patients begin to discover that more is wrong than they have been accustomed to. Their asthenia, heretofore comparatively bearable, becomes very much more aggravated; they are much more toxic and their appearance may approximate quite closely that of the patient with myxedema. They have a dull headache in the morning on rising; their joints crack and sometimes are quite painful; their skin is rough and dry, and the appendages of the skin—the hair and nails—are brittle and have lost their usual pliability. Constipation is the rule and digestive conditions are very much aggravated. In other words, they begin to find added to all the usual troubles of the sufferer from tuberculosis another series which are dependent upon hypothyroidism. Here the thyroid gland has been stimulated gradually and persistently until it has been played out and as a result of these long continued stimuli we have a condition of thyroid inefficiency which varies in degree and consequently in the character and extent of its effects upon the body.

"To me the condition of infiltration which is so usually present in hypothyroidism is worth a little more extended consideration than has seemed to be the case in the literature on tuberculosis. It will be recalled that Hertoghe, of Antwerp, has emphasized the importance of the infiltration which always accompanies hypothyroidism and is serious in proportion to the degree of thyroid inactivity. Since the thyroid hormone stimulates the cell chemistry, a lack of this hormonic stimulus spells slowed cellular activity with an accumulated toxemia which disturbs the chemical changes going on in the cell structure. The retained wastes increase the density or concentration of the cell fluids and they draw

to themselves, from the blood and tissue fluids, enough plasma to equalize the intracellular osmotic tension with that of the blood. A puffiness and swelling ensue, due to the natural physical changes expected under such circumstances. This is the so-called 'thyroid infiltration,' and it is indeed an important element in many a disorder.

"Naturally this infiltration influences circulation very definitely and consequently the resistance of the body to disease, which depends in a very large measure upon a satisfactory circulation, is lowered. The lung is not immune to the influences of the thyroid and this condition of infiltration—which decidedly affects the skin, the alimentary canal, the larger organs of the body and, in fact, the whole organism—must cause some changes in the lung, *as a result of which the capillary circulation is mechanically lessened* and the extremely important chemical exchanges of oxygen and carbon dioxide by the blood are lessened. So in addition to the general lack of cellular oxidization due to the thyroid insufficiency there is an equally important deficient chemistry due to the slowed gaseous exchange. Naturally this must have a serious influence upon the general conditions in tuberculosis and besides this it must also exert a local influence upon those responses which the body makes in the lungs to the invasion by the organism involved.

"It will be seen, then, that both hyperthyroidism and hypothyroidism are likely to be found in tuberculosis; the former occasionally and most frequently in the early cases and in the most healthy individuals; and the latter more commonly in the cases of longer standing and in individuals in whom toxemia from various sources has lessened materially the body's capacity to respond in the usual manner in which the body resists disease.

"I have made a number of observations on quite a few cases and have come to the conclusion that hypothyroidism is probably nine times as frequent as hyperthyroidism in the average run of cases of chronic pulmonary tuberculosis, and consequently no further consideration will be given in this paper to the condition of hyperthyroidism as it may influence the treatment of tuberculosis save to say that since hyperthyroidism is practically always due to toxemia, no matter whether it is focal or otherwise, every effort should be made to detoxicate and to sedate the thyroid and the sympathetic system by means of suitably fitted together organotherapeutic products. Parenthetically, I may remark that pancreas gland is an excellent

sympathetic sedative. In addition to this, adrenal substance sometimes is very efficient in overcoming the asthenia resulting from hyperthyroidism, and a combination of these originally evolved by Crotti (known as *Pancreas Co.—Harrower*), has been used successfully by me for a long time in hyperthyroidism. It is just as valuable in tuberculosis where a hyperthyroidism may be prominent.

"The conditions of hypothyroidism, on the other hand, are so commonly present in tuberculosis that it seems to me a very unfortunate thing that the profession so uniformly ignores the endocrine glands and confines its efforts largely to the hygienic, tuberculin and dietetic treatment of tuberculosis. All these measures are good and worthy to be commended, but when there is a well defined endocrine aspect to any case, no matter whether it may be tuberculosis or not, every effort to treat other conditions which involves the ignoring of the underlying endocrine bases, is going to fail in proportion as it ignores these vital elements.

"In other words, the tuberculosis patient should always be studied from the standpoint of the endocrine glands and particularly the thyroid. By means of my Thyroid Function Test it is very easy to determine whether an individual's thyroid function is apathetic or unusually sensitive. The use of this test in a number of cases has shown that the thyroid gland does not respond to the step-ladder dosage of thyroid which constitutes the test, and when the obvious treatment is applied—support of the played-out thyro-adrenal system—noticeable changes for the better frequently have followed. I do not mean that to encourage a depleted thyroid or to increase cellular chemistry necessarily is a cure for tuberculosis—far from it; but to ignore the support of these glands when depleted, no matter what other treatment may be given, is to pass by a very rational and useful measure.

"The application of this idea is neither empirical nor unscientific. It is logical to presume that a gland with functions as important as those of the thyroid which are involved so definitely in every case of infection and toxemia necessarily must eventually become overworked, and when the endocrine glands are overworked we have hypocrinism; and in this instance, hypothyroidism. We admit that thyroid therapy is a useful measure in obvious cases of hypothyroidism as cretinism or myxedema, but we have been frequently in the habit of overlooking the minor forms. They are just as important, or even more so.

"If the thyro-adrenal system is depleted and we support it with *Adreno-Spermin Co.* (*Harrower*), we increase oxidization, we stimulate cellular chemistry, we favor the immunizing response of the body and nutrition, and in every way encourage those very factors upon which we depend for the body's response to such other treatment as may be given simultaneously."

SECTION V. CHAPTER 4

PLURIGLANDULAR THERAPY IN THE FUNCTIONAL NEUROSES

A neurosis is said to be a disorder of the nervous system not dependable on any discoverable lesion; and since there is no obvious organic change, it is natural to presume that practically all neuroses are of the functional type. There are a number of neuroses that enter into and complicate the work of the general practitioner in the most disconcerting way and involve the treatment of many cases very decidedly. Perhaps the most common of these is known as the "fatigue neurosis," a neurotic condition due to nerve tire, otherwise known as neurasthenia or psychasthenia. The subject of asthenia already has been given considerable attention in this book, and I hope it has been shown to be connected with adrenal dysfunction; for neurasthenia is likely to be profitably considered from the standpoint of the internal secretory organs, and particularly the adrenals.

Butler's Notions about Functional Diseases. An interesting statement by the late Dr. George F. Butler (*Am. Jour. Clin. Med.*, 1918, p. 679) may be quoted here: "The peculiar characteristic thing about the physiologic pathology of all the functional nervous diseases is that the neurons themselves are not primarily at fault. They are merely scapegoats. They bear the brunt of some other morbid condition, and the nervous disturbance is an end-result. A quality that is common to them all is a certain irritability and spasm, due not to a positive exaggeration of function, but to a sort of negative disability. The neurons may be likened to a workman fretting because of a lack or poor quality of tools; and one might as well expect to get good work out of the workman in such a plight by drugging him into stupefaction as to expect to remedy the neuroses with narcotics.

They merely add one form of toxicosis to another. The essential morbid state in all of these diseases is that of a nervous revenue which is not adequate to the ordinary demands of living. The rational principle of treatment is to bring the expenditure as far as possible within the income, either by decreasing the former or by increasing the latter, or both. In one sense they are the most obstinate of all nervous ailments, for, as intimated, these patients usually inherit their neurotic tendencies, and one has to do with the complex ramifications of biological stresses and strains. They are physical ne'er-do-wells, just as some persons are financially shiftless. It is almost as impossible to make solid, prosperous individuals out of either type as to change the leopard's spots. The most that can be done, with the physical as with the economic ne'er-do-well, is to educate and help them to live within their modest income."

Sympatheticotonus and Vagotonus. In the last few years, two new terms have crept into current medical literature—sympatheticotonus (sympathicotonus) and vagotonus. As the names indicate, the former is a condition of tonicity resulting from overaction of the sympathetic nervous system, whereas, on the other hand, vagotonus is the result of irritability of the vagus or pneumogastric nerve. It happens that the functions of the vagus are antagonistic to those of the sympathetic; hence, vagotonus is virtually the opposite of sympatheticotonus. Both of these conditions are allied to neurasthenia and unquestionably are connected very closely with disturbances of the glands of internal secretion. In the former instance—sympatheticotonus—there is an unusual irritability of the adrenal glands with hypersensitiveness of the sympathetic and general overwork of all the organs involved and controlled by this mechanism. Naturally, sympatheticotonus will last either until it is controlled by proper therapeutics or until the organs that are played upon by the sympathetic impulses "give up," in which case the opposite manifestation, or vagotonus, will obtain.

In my estimation the whole subject of the diagnosis and treatment of these intangible nervous manifestations may be considered with greater satisfaction from the standpoint of the endocrine glands. For instance, we know that the adrenal system is intimate in its control of the sympathetic nervous system; hence adrenal irritability which will cause sympatheticotonus will also be the underlying cause of vagotonus, provided this irritation is allowed to go on far enough or until the adrenals can stand it no longer and

"play out." Of course, those factors which influence the adrenal glands and, for that matter, the other glands of internal secretion, must be considered in our study of either an increase or deficiency of sympathetic tone. For example, it is well known that neuroses of this character result from fear and its twin brother, worry. In fact, nothing has done so much to establish a reasonable working basis of the cause of neurasthenia and to explain some of the remarkable results that have been secured from the treatment of conditions of this character by means of organotherapy than the work of Walter B. Cannon, at Harvard University, in which he has shown that the emotional factors so common in health and disease, including pain, hunger, fear and rage, brought about many of their ordinary physiological reactions through a direct influence upon the adrenal glands. This explains many things in our every-day experience, just as it does many other things in clinical practice, especially in the functional side of neurology.

The Endocrine Aspect of the Neuroses. It is a fact that cannot reasonably be denied that most neurotic conditions are commonly associated with various endocrine disturbances. Many neurasthenics habitually complain of sensations of cold. Nervous chills are not uncommon and cold hands and feet, indefinite muscular pains and an exaggerated sense of physical exhaustion as well as mental inertia, are the rule in neurasthenia. These are also typical endocrine findings. M. Allen Starr, of New York (*Med. Record*, June 29, 1912), connects such neuroses with dysthyroidism or at least errors of the endocrine system as a whole with more prominent manifestations of the thyroid and adrenals. He continues his description of these cases thus: "Certain neurasthenics are extremely restless and active both mentally and physically, though unable to keep their minds on one subject for any length of time. They are usually anxious about their condition, and experience a sense of heat in their body which prevents them from remaining in warm rooms. Their eyes are bright, their skin shiny and moist, their hair glossy and they are usually thin. Other typical features are tremor about the hands, exaggeration of the knee-jerks, abnormal sensations of hunger, diarrhea and excessive menses. They sleep badly, are hypersensitive to sounds and often complain of sudden flashes of heat. The pulse is often abnormally frequent, 80 to 90. In such neurasthenics as these suspicion should be awakened that there in an excess of secretion of the thyroid gland. . . ."

Here the Thyroid Function Test mentioned elsewhere (Sec. IV, Chap. 4) may be of much service, for such sympathetic irritability may be of adrenal origin or, at least, not a minor form of hyperthyroidism. Treatment calculated to sedate the sympathetic irritability simultaneously with a search for cause, with its later eradication, is much more likely to be satisfactory than to ignore the endocrine element entirely—a thing which has been quite common heretofore.

Neuroses of Gonad Origin. Among the most common endocrine neuroses are those associated with ovarian dysfunction, either during puberty or the menopause, or the thirty-year period in between. It is very well understood that menstrual difficulties, menopausal derangements and disturbed functional activity of the ovaries and associated organs cause neuroses of all shades, from a slight "fatigue neurosis" to a "fear neurosis" which may even metamorphose into insanity. As a matter of fact, the so-called "ovarian psychosis" is well understood as being due to disturbed ovarian activity, and many times it is amenable to treatment calculated to regulate the disturbed endocrine balance. *In other words certain insanities are cured by organotherapy.*

Again, the large class of sexual neuroses dependent upon overwork or abuse of the gonads may show themselves in diverse nervous, circulatory and temperamental manifestations and yet, fundamentally, be due to the original derangement of the function of these glands.

With these few points in mind, we are led to acquire an attitude in regard to the etiology, and hence to the treatment of neurotic conditions, which enables us to class them prospectively as disturbances of internal secretion, and likely to be amenable to those methods of treatment known to control disorders of this character. To recapitulate: *There may be an effective organotherapy of many neuroses and psychoses.*

As one prominent neurologist once said to the writer, "In so many of these indefinite nervous cases, we neurologists find ourselves up against a stone wall with no chance to scale it, and about the only alternative is to turn around and retrace our steps. This idea of yours [the idea is far from being my own, I have merely picked it up in my reading, and shouted about it a little louder than some of my colleagues—H. R. H.] offers us some hope in these very cases. and I would not be surprised if the endocrines would serve as a sort of a scaling ladder to get over that terrible blank

wall." This was a number of years ago, before a good many recent reports and opinions had been published on the subject, and it really seems that the vision of this neurologist is being realized and that the difficulty, likened to the impossible, unscalable wall, many a time is being surmounted very satisfactorily.

The principal point that I desire to make concerns the importance of a possible endocrine factor in neuroses.* I do not need to quote many authorities and fit together a plexus of statements by various men prominent in the profession. The fact remains that the endocrine aspect of the neuroses is the most encouraging of all.

Alimentary Neuroses. Toxemia and disturbed adrenal functioning react directly upon the digestive tract. Pottenger, of Los Angeles, who has done much profitable work on the relation of the endocrines and the sympathetic system to tuberculosis, makes the following statement (*Jour. A.M.A.*, Jan. 8, 1916): "The adrenal glands are supplied through the splanchnics; and impulses which cause a general sympathetic stimulation stimulate these glands also. A minute amount of adrenin poured into the blood stream has the effect of producing a prolongation of the condition which is brought about by direct sympathetic stimulation; thus adrenin will cause a dry mouth, impaired digestion, intestinal stasis and a rapid heart. That toxemia, like the emotional states, acts by stimulating the sympathetics and by prolonging the action through the stimulation of the adrenals, seems quite certain."

Upham, of New York, in a consideration of mucous colitis (*N. Y. Med. Jour.*, Sept. 21, 1918) calls attention to the sympathetic-vagus balance in alimentary disorders as follows:

"It has been amply demonstrated that stimulation of the vagus in health produces motor activity along the gastrointestinal canal. This activity is held in check and controlled by the inhibition from the sympathetic nervous system. The wonderful phenomenon in this occurrence is the nerve balance in the normal individual, whereby stimulation is combated by just enough inhibition to produce a condition of nervous balance with resultant normal functioning of the

*The second issue of *Harrower's Monographs on the Internal Secretions* is entitled: "Neurasthenia: An Endocrine Syndrome," and contains a wide range of information culled from many sources which will make interesting supplementary reading. (92 pp., price, $1.25; annual subscription, $3.00)

gastro-intestinal system. But in an individual who has an over-active vagus, which may be due to an excess of nerve activity of that structure, there occurs a series of spasmodic activities throughout the gastro-intestinal canal. These spasmodic activities, when in the stomach, produce areas of ischemia and are the foundation of deficient circulation which makes possible the location of infection from any systemic source and the production of gastric ulcer. The same series of phenomena occurs in the large intestine; a condition is brought about which gives rise to spasmodic contractions of the colon, which are features of the condition of mucous colitis." Here we have a plausible explanation of two phases of neurasthenia which are unusually resistant to treatment—until the endocrine aspect is appreciated.

The Search for Dyscrinism in the Neuroses. If, then, we will consider every sufferer with a functional neurosis from the standpoint of the internal secretions, we will immediately busy ourselves with finding and controlling ovarian dysfunction, if it happens to be present, with the study of the patient from the standpoint of the thyroid gland, with its paramount control of detoxication and cell chemistry in general and with at least a thought about the adrenals, which are very likely to be unusually irritable or past that stage, in which case we will attempt to modify the underlying causes of this irritation, either toxic, endocrine or emotional. And if matters have reached the stage where there is a well-defined adrenal insufficiency—*and this is perhaps the most common single endocrine manifestation in individuals suffering from neuroses*—we will establish its presence to our satisfaction by the study of the blood pressure, which will be found to be unusually low; the temperature, which is often subnormal; the elimination, especially of the urinary wastes, which are usually much below par; and of the nutrition, which ordinarily is poor; and then if we can consistently make ourselves believe that a given neurasthenic patient is also suffering from hypoadrenia, we will do the next obvious thing *and treat the hypoadrenia*—not the neurasthenia. All this sounds well enough, but it is "not the thing y'know," as they are wont to say in England. But if my own experience is any criterion, we will be surprised many times at the remarkable change made, not merely upon the obvious physiologic factors controlled by the adrenals and the glands associated with them but upon the patient's view of life, general health, and especially what some are pleased to call his "pep."

Again, if any other endocrine element obtrudes itself, surely the right thing to do is to go after it "hammer and tongs," and the principle that is invariably followed in all navies—clear the decks before action—is the best and only policy to follow in these particular cases. If there are disturbances of these glands in the nature of insufficiencies or otherwise, we have something with which to occupy ourselves very tangibly; and since the organotherapy of endocrine disorders is altogether the most satisfactory branch of therapeutics, after we remove some underlying element which happens to be causative, before very long, in addition to reëstablishing the condition toward which we are directing our treatment, we find that the neurasthenia is also responding.

The moral of this little sermon is simply this: Find an endocrine element in your neurasthenic patients and treat it, and you may be surprised at the ease with which a stubborn and intractable symptom-complex fades away.

Some Practical Therapeutic Deductions. Naturally the endocrine treatment of neuroses differs with circumstances. If there is ovarian dysfunction in the nature of an endocrine insufficiency with disturbed menses, a protracted wait between the periods, a materially reduced flow with various associated nutritional, nervous and circulatory disorders, use the formula No. 4, *Thyro-Ovarian Co.* (*Harrower*), in the expectation that physiological stimulation of not merely the ovaries but the associated endocrine glands may reëstablish ovarian function and, at the same time remove a part or all of the foundation of the neurasthenia. The same thing applies to disturbances of this character at the menopause. Here a factor to which the body has accustomed itself for many years is removed, and there is a resulting disorganization of the whole hormone balance. Mitigate this removal by adding a little to the suddenly reduced quantity of hormones, and it will be found that the circulatory and nervous conditions clear up in a most remarkable fashion. On the other hand, if the ovaries seem to be irritated, the length of time between the periods is reduced, and the amount of flow considerably increased with obvious signs of pelvic pain and discomfort, antagonize this ovarian hyperfunction by using mammary substance as represented, for example, by No. 38, *Mamma-Ovary Co.* (*Harrower*) in young women with a functional difficulty, or No. 40, *Mamma-Pituitary Co.* (*Harrower*) in older women with a heavier flow and more chronic trouble; and

in addition to reducing the immediately obvious symptom—menorrhagia—the associated neurotic manifestations usually disappear with it.

The same thing applies in the male. Prostatic difficulties are very commonly associated with neurasthenia and quite frequently remedied very nicely by applying the same fundamental principles as those just mentioned; for instance, the formula No. 48, *Prostate Co.* (*Harrower*) not merely has been known to reduce local prostatic hyperesthesia and mechanical difficulties resulting from prostatic hypertrophy but to clear away at the same time the morbid neurotic state which may be dependent in a large measure upon deranged physiology of these glands.

I have already discussed the adrenal factor in neurasthenia ("The Adrenal Glands in Health and Disease," Sec. IV, Chap. 5), and many ideas of others have been gathered together to establish the underlying importance of the adrenal glands in fatigue neuroses. The subject has been given even further consideration in a book which I published in 1919, entitled, "The Adrenal Glands in Every-Day Medicine," which is now out of print, and in the fifth (January 1922) issue of *Harrower's Monographs on the Internal Secretions,* which is a collection of data from scores of sources emphasizing the reality, frequence and clinical aspects of "Adrenal Insufficiency." (120 pages; $1.50 postpaid; annual subscription, $3.00.)

Suffice it to say that the physician who gives to the neurasthenic with obvious hypoadrenia, treatment of the ordinary character which does not include a definite effort to reëstablish the disturbed endocrine function, is destined to more frequent failure than the one who believes in a treatment which includes this with all other indicated measures. This is the reason for many splendid results from the use of my *Adreno-Spermin Co.* in neuroses. The adrenal glands are supported, and functions associated with these glands are simultaneously encouraged. As a result, the low blood pressure is increased, the subnormal morning temperature is raised and with it the whole chemistry of the body, and, as a result of that, the elimination is measurably enhanced—I have seen a twenty-four hour urea figure as low as .8 per cent. and after a month's treatment found it 1.75 per cent, whereas the normal is probably about 2 per cent. With all these changes there ought to be a marked change for the better in the neurasthenia, which heretofore may have been treated by burdening the emunctories

and paralyzing the nerve endings with bromides or allowing matters to slide, by prescribing what is often erroneously called a rest or change of air.

Functional Endocrine Neurasthenia. At a recent meeting of the British Medical Association, held June 1921, at Cambridge, England, Dr. Arthur F. Hurst, physician and neurologist to the famous Guy's Hospital, London, called attention to the fact that a special effort must be made to gain a clear conception of what is meant by such terms as functional neurosis, psycho-neurosis, neurasthenia, etc. In his opinion a functional disorder was one which did not depend upon organic change; it might be either biochemical or nervous in origin. Neurasthenia generally has been classified as a neurosis, but it really depends upon definite, though evanescent, organic changes in the central nervous system and in the adrenals and possibly other endocrine glands resulting from mental and physical exhaustion and chronic intoxication. According to Dr. Hurst, therefore, neurasthenia is really a temporary organic condition and not a functional disorder.

From the writer's personal standpoint neurasthenia is still a functional neurosis, merely because, despite the fact that the endocrine glands are very definitely involved in its etiology, the influence is of a temporary functional character and the changes in either the nervous system or the endocrine system do not seem to be a structural variety. When there are definite anatomical changes in the organism we speak of them as organic. When, however, there is a change in the activity of an organ doubtless the condition is purely functional.

When those factors which are known to deplete the endocrine glands, and especially in the instance under discussion, the adrenal system, result from mental as well as physical exhaustion and chronic toxemic conditions, obviously the change in the adrenal glands does not necessarily have to be organic in character and, therefore, its influence upon the central and sympathetic nervous system is equally functional.

While I differ with Dr. Hurst, and I think that many of my readers will agree with me, there is a great deal of importance to be laid on his reference to the influence of various forms of exhaustion and intoxication upon the adrenal system, and therefore, that many such individuals fundamentally are cases of neurasthenia of endocrine origin.

Tom Williams, of Washington, and a good many other

aggressive neurologists in this country and France have very definitely connected the adrenal glands with the origin of neurasthenia. Toxemias of all varieties—those due to improper diet, as for example, the use of coffee and excessive amounts of meat; from putrefactive products of disturbed alimentary function; from foci of bacterial infection in various parts of the organism; and also the product of a deficient endocrine activity of the thyroid gland, which is responsible very largely for maintaining the normal chemical activities of the cells of the body and keeping the metabolism up to par, and finally the abnormal toxemias due to nervous exhaustion, i. e., mental overwork, general cellular overwork and, therefore, an excessive fatigue syndrome—all exert the same fundamental influence upon the adrenal glands. They overstimulate them and this stimulation very uniformly results in depletion, with a resulting hypoadrenia, which is so commonly a part of the usual syndrome of neurasthenia. In addition to the usual neurasthenic manifestations which are so uniformly found, we expect to find changes in the systolic blood-pressure—the sphygmomanometer sometimes showing a blood-pressure of 100, 90, or even 80 millimeters—lessened elimination of the urinary wastes and especially the 24-hour urea, lowered general chemistry as manifested in malnutrition and a subnormal temperature and, finally and most important, a tendency towards asthenia of a most aggravated type.

These cases need detoxication. They need a diet which will prevent the ingestion of as many as possible of the poisons which are known to stimulate the adrenal system. They need rest and a change of environment in order that the disturbances of the mind and brain may be reduced to a minimum, so that the emotional factors, which so often cause adrenal overstimulation, can be modified.

Finally and, to my mind, as important as any single measure in the treatment of these neurasthenias, I urge functional support of the adrenal glands by means of organotherapy. It is possible to replace, in a large degree, the principles that the adrenal glands are not supplying as much of as they should, just exactly as one can supply a missing thyroid hormone or the principle from the ovaries. This has been done many hundreds of times by the use of a formula containing adrenal substance (total gland including the cortex), a small dose of thyroid with spermin and glycerophosphate of calcium. I am proud to be able to associate my name with the origin and preparation of

this excellent pluriglandular support, which is used with advantage in practically all forms of neurasthenia.

There is a large and growing bibliography of communications which support the position that I take in this matter. Some of these authors are convinced and obviously enthusiastic about "a new find," while others seem to be reluctant to admit that our estimate of the etiology and treatment of the neuroses must be revised radically. We read such things as this: "All these *seem* to point to a *possible* relation between the neurasthenia and . . ." etc.—and we feel justified in smiling to ourselves and recalling some patients who "seemed" to be quite pleased when they last reported.

It has been said by Tom Williams, of Washington, that the word "neurasthenia" is a cloak to cover our shortcomings in diagnosis. He is right, and I believe that this neurosis properly might be called an "endocrinosis," if such a new word is permissible.

SECTION V. CHAPTER 5

THE TREATMENT OF OVARIAN DISORDERS

Functional ovarian disorders include developmental, menstrual and climacteric disturbances and represent a very large proportion of all the diseases of women. We have seen in the section on Diagnosis that the ovaries are responsible for many factors in the normal development and functioning of the body and that they themselves are intimately associated with other glands of internal secretion, notably the thyroid and pituitary.

As has been explained, there are two chief classes of ovarian dysfunction—insufficient endocrine activity and hypersecretion. Since the ovaries play such an important part in the essential changes known as secondary sex characteristics, any ovarian insufficiency that manifests itself before development is complete will cause more extensive results.

Functional Ovarian Insufficiency. As a result of various causes, nutritional (hormonic), nervous and circulatory, ovarian function may be insufficient. I think this is quite the commonest glandular insufficiency among women, unless perhaps we should give first place to the adrenal insufficiency which follows toxemias, acute infectious disease and

shock. At all events, hypo-ovarism is a most useful finding in general practice and the chief results are amenorrhea, dysmenorrhea and the various neuroses resulting from these disturbances. The treatment of ovarian insufficiency with organotherapy is one of the accepted organotherapeutic procedures, and while there is some difference of opinion as to the relative merits of glandular extracts of the corpus luteum or total ovary, there can be no doubt that the principle of homostimulation fully outlined in the second section of this book may be applied with great advantage in the control of conditions of this character.

For fifteen years or more, functional pelvic disorders and the reflex disturbances resulting therefrom have been treated with corpus luteum or ovary alone, and for obvious reasons no method or drug can begin to take the place of such preparations, merely because the same principle applies that does in hypothyroidism—the body is not making enough of a certain substance and is suffering from the lack of the stimuli made possible by that substance; we intervene by securing a similar substance from animals, administer it to the patient, and the body is able to take it up and use it to reëstablish its own affairs. Hence, extracts of this character not merely stimulate the gland which corresponds to that from which it was made, but replace, in a degree, the hormone that may be lacking.

Numerous clinical experiences by literally hundreds of physicians now connect the thyroid gland with the ovaries. A number of quotations from a communication by Oliver T. Osborne emphasizing this fact will be found in the other chapter on the diagnostic aspects of ovarian disturbances (Sec. IV, Chap. 8) which, by the way, should be read in conjunction with these remarks. Suffice it to say that hypothyroidism and hypo-ovarism go together clinically and deserve to be treated together organotherapeutically.

When I was in Paris in 1913, I learned that Prof. Paul Dalché, of the Hôtel Dieu, was in the habit of routinely adding a centigram a day of thyroid extract to the ovarian treatment of menstrual difficulties, the reason being that sometimes the ovarian difficulty was really of thyroid origin more than of ovarian origin, and while direct ovarian stimulation might be good, a consideration of the associated and causative elements at the same time would be much better.

The same principle applies in regard to the pituitary gland. We know that pituitary insufficiency causes ovarian

insufficiency; hence, if we have a case of functional hypo-ovarism, how do we know that there is not underlying it a pituitary insufficiency? And, on the principle which I have outlined in my hypothesis of hormone hunger (see Sec. II, Chap. 5), the body is capable of making the most use out of the things that are given to it in proportion to the respective needs of the various organs which may be involved in the symptom-complex.

The Thyroid-Ovarian Relations. A recapitulation of my own opinion of the close relationship of the thyroid gland and the ovaries, based on personal experiences, is as follows: The thyroid hormone is largely instrumental in establishing gonad function. One of the chief causes of the not infrequent enlargement of the thyroid at puberty is that it has a much larger job to accomplish for the moment, and, lacking the capacity to do it without structural change, it hypertrophies temporarily in an effort to render its best service. Again, hypothyroidism indeed favors amenorrhea, and one of the commonest results of the minor forms of hypothyroidism is a change in the amount and frequency of the menses, tending very commonly toward amenorrhea. To my way of thinking, this is because the ovaries are in the habit of demanding of the thyroid a certain hormone, or arousing influence, which, because of some additional work set upon the thyroid, perhaps in the nature of detoxication or of some other endocrine demand upon its capacity, has either diverted the thyroid assistance or actually lessened it. I believe that the best proof that this position is based upon good grounds is the fact that *thyroid therapy so very often is useful in amenorrhea.* Dalché, as we have seen, believes that the thyroid encourages ovarian activity, and that thyro-ovarian therapy is more efficacious than either of these two single organotherapeutic measures—ovarian and thyroid.

The reciprocal relations between the thyroid and the ovaries are unquestioned. I have seen many cases of hypothyroidism that have been benefited materially by arousing the ovarian activity which was simultaneously deficient. My experience is sufficiently extensive—I am fortunate indeed in having many correspondents throughout the world, some of whom see fit to bring their troubles to me for consideration—to have found cases in whom a hypothyroidism had been treated with comparatively unsatisfactory results, and lo and behold, the simultaneous consideration of the associated ovarian trouble touches the miraculous button

which sets things right. Hence, there must be some relation between the reëstablishment of an ovarian activity and the control of an associated thyroid trouble. In other words, it is not always the thyroid that is entirely responsible in ovarian troubles, but the ovaries may be partly responsible for some of the troubles in athyroid conditions. The wisest way, after all, is always to consider these glands together, which my readers know full well I have urged times without number.

Pluriglandular Ovarian Therapy. The Boston gynecologist, William P. Graves, in a paper read before the American Gynecological Society in 1919, reports that the general tonic effect of organotherapy was especially present when other pluriglandular disturbances accompanied the ovarian insufficiency. He says, "The stimulating effect of the ovarian residue could sometimes be enhanced by the addition of thyroid and the anterior lobe extracts."

If you have a given endocrine dysfunction involving the thyroid and ovaries, *treat them together*—the selective capacity of the cells will determine how much and how quickly your endocrine remedies are appropriated (or not, as the case may be)—and, needless to say, the confidence that was initiated by my experience in Paris, and the things which I saw and heard there, and have read since, have been multiplied a thousand fold by the most flattering comments that one could really ask for, sent to this office about the comparative advantages of the *Thyro-Ovarian Co.* (*Harrower*) over thyroid alone or corpus luteum alone.

As this is read for the printer, a physician in Seattle writes asking if I have seen a paper in the *New York Medical Journal* (Oct. 5, 1921) by John C. Hirst, of Philadelphia. He advises me to read this statement for my encouragement:

"We are only at the threshold of the problem of all the glands of internal secretion. I believe that future development will be along the lines of pluriglandular therapy, due to the probable correlation between the pituitary, thyroid, mammary gland, suprarenal, and ovary, rather than in the use of single extracts. Especially will this hold true in the developmental anomalies of the genitalia."

Amenorrhea of all shades, as well as dysmenorrhea, and many of the intangible circulatory and nervous disturbances associated with these disorders are quite the most satisfactorily treated by pluriglandular therapy, for the reasons already given. For years I have been using with

marked success a formula now called No. 4, *Thyro-Ovarian Co.* (*Harrower*), which contains, in addition to ovarian substance with corpus luteum, a small dose each of desiccated thyroid gland and total pituitary substance. It is recommended as a part of the treatment of the usual functional pelvic derangements of ovarian origin and is believed to excel corpus luteum alone, merely because the luteal function is practically never involved exclusively.

Routine Administration of Thyro-Ovarian Co. Since the ovarian hormone function is cyclic and varies considerably during the month, one can increase the value of this pluriglandular formula by arranging the dosage so that it is omitted at certain periods and pushed when likely to have the widest physiological effect. Incidentally, this is quite a convenience to the patient and, at the same time, reduces the expense of the treatment. Prior to the consummation of this monthly task—at the very time when the nervous and circulatory difficulties which accompany amenorrhea are greatest—we can reënforce the hormone function in proportion to the needs by increasing the dose; hence I have suggested the following cyclic method of administering *Thyro-Ovarian Co.* which has proved very satisfactory: Instruct the patient to omit the remedy entirely for a period of ten days following the onset of the menstrual flow. This includes the whole menstrual time, which is believed to be just after the time when the ovarian endocrine activity has reached its monthly peak. During the next ten days, i. e., the middle of the month, one 5-grain dose is given three times a day, while for ten days or a week, depending upon circumstances, immediately before the next flow the dose may be pushed or doubled. This is again stopped as soon as the flow shows itself; and since there is but a short time during each menstrual month that the ovaries can be stimulated effectually and this organotherapy is a means of reëstablishing a normal cellular activity, such treatment should be continued for a number of months, and if the results are good—and very commonly they are splendid—it should be continued for some little time after an apparent cure has been secured.

Menopausal Difficulties. The disconcerting circulatory disturbances connected with the change of life, and enumerated elsewhere, are evidently due to the same sort of a cause as other forms of amenorrhea earlier in life and respond very satisfactorily to the replacement of a part of the necessary quantity of ovarian hormones. In the climac-

teric especially, the value of pluriglandular therapy should be obvious, for it is well known, for instance, that during the decade between forty and fifty, serious forms of hypothyroidism in women are most common and that the menopausal difficulties are by no means entirely of ovarian etiology.

Neuroses, Psychoses and Insanity. Unfortunately, in some remarkable manner the imbalance due to dysovarism may cause more or less serious disturbances of a mental character, and one of the dreaded results of severe ovarian dystrophies is insanity. We prefer to call it "ovarian psychosis" and, irrespective of the complexity of the cause, to attempt its treatment by the regulation of the ovarian difficulty that shows itself simultaneously. In other words, an ovarian psychosis may respond to ovarian therapy just as other less serious nervous conditions; and while the prospects are not so good because the trouble is more serious and comprehensive, in its effects, they are better than in the treatment of the other forms of psychosis. This means that mental disturbances in women that may be connected with ovarian dysfunction may be modified favorably by direct attention to the accompanying ovarian disturbance. A number of experiences of this character following the use of my *Thyro-Ovarian Co.* have been brought to my attention, one case being particularly interesting. I was surprised to receive a letter from San Diego in which the following sentence appeared: "I am getting some wonderful results. One young lady who was diagnosed as suffering with dementia precox, has made a complete recovery. They sent this lady to a sanitarium and paid out about seven hundred dollars with absolutely no apparent benefit. I put her on the *Thyro-Ovarian Co.*, and sent her up into the mountains. One month did the work. She does not even have a suggestion of her former trouble." I immediately wrote the doctor that I did not believe that the case could have been properly diagnosed and that the condition evidently was an ovarian psychosis and not dementia precox. Eleven months later, I had occasion to visit this physician and learned, to my pleasure, that there had been no recurrence of the mental aberration and that the young lady was in better health than at any time previously.

Organic Ovarian Insufficiency—Infantilism. If for some reason (usually associated with insufficiency of the thyroid or pituitary, or both) the ovaries do not develop and the internal secretory function of the corpora lutea does not

materialize at the ordinary time, i. e., at puberty, there will be no menstruation. In addition to this, the growth and development of the essential reproductive organs, including the uterus and ovaries themselves and the external genitalia, as well as the breasts, will be prevented. This condition is known as hypoplasia, status hypoplasticus, or infantilism; and while there are some prospects for its treatment, obviously they are not so good as in less serious disturbances that show themselves later.

The treatment of infantilism is not an encouraging proposition. It should involve a study of the possible causes in other ductless glands, including a test of thyroid function, a study of the pituitary gland, both from the standpoint of the radiographic examination of the sella turcica and the measurement of sugar tolerance, etc., and search should be made with the fluoroscope for a persistent thymus. All of this, in addition to the careful study of the whole body, as well as a pelvic examination if this is at all feasible. It is essential to strip the patient because infantilism does not necessarily involve developmental difficulties alone— it is quite a different proposition from cretinism, although infantilism is one of the symptoms of cretinism—while it does cause definite changes in the form and distribution of hair. If the usual pads of fat on the hips and, generally speaking, the feminine contour as seen from behind is absent, and the axillary and pubic hair is considerably lessened or entirely absent and mammary development does not appear, or is defective, in all probability we have a case of true infantilism. There are only two things to do in cases of this character: first, to remove any obvious causes of the trouble as, for example, malnutrition or a persistent thymus; and second, to homostimulate not merely the ovaries which may be present in a rudimentary form, but also the glands which control ovarian function and in which a disturbed internal secretory activity may be taking place which may be the underlying cause of the difficulty. Hypopituitarism and the more serious forms of hypothyroidism both may bring this about, and the only treatment worth considering is endocrine treatment. Such organotherapy should consist of the persistent administration of pluriglandular formulas including the thyroid, pituitary and ovary (i. e., either No. 4, *Thyro-Ovarian Co.* (*Harrower*), or No. 73, *Gonad-Ovarian Co.* (*Harrower*)—a similar preparation to No. 4, to which a generous dose of anterior pituitary substance has been added). The dosage must be continued for a long

period and may be supplemented by other circulatory stimulating measures like hydrotherapy and osteopathy. In fact, I know of several cases of infantilism that seem to have been very materially benefited by the neuro-circulatory changes which have resulted from intelligent spinal manipulation.

Ovarian Irritability—Hyperovarism. Fortunately, the most common functional disorder of the ovaries is an insufficiency, and the opposite condition is comparatively rare. I say "fortunately," because hyperovarism is a more serious and more difficult disorder than its physiological opposite, just as thyroid excess is more difficult to handle than thyroid insufficiency.

Ovarian irritability is clinically evident when there is marked pelvic congestion and discomfort with menorrhagia (both forms—prolonged and excessive menses, and too frequent periods), and sex irritability, which may show itself as erethism, nymphomania, or even insanity.

The cause varies—often it is the result of structural change, or, again, it is purely functional, and the result of mental or sexual stimuli. Pelvic infections are prominent in the etiology of this condition, just as foci of infection are among the commonest causes of hyperthyroidism.

The treatment is not easy, for usually many of the factors involved are beyond the physician's control. Depletive local treatment is good, especially when the uterus is large and boggy. I advise magnesium sulphate gelatine tamponade for several weeks. Psychic control is especially needed where introspection, mental sex stimulation and incomplete intercourse are discovered on questioning. The Robert W. Chambers style of "literature" has caused menorrhagia in girls and young women, and the treatment is—"Cut it out for good."

The most satisfactory organotherapy is mammary substance. This is the physiological antagonist to ovarian function just as the mammæ and ovaries normally antagonize one another. The whole subject of mammary therapy is considered fully in Sec. V, Chap. 9, "The Control of Menorrhagia."

Two formulas on my list are recommended in menorrhagia and hyperovarism. No. 38, *Mamma-Ovary Co.* (*Harrower*), for girls and young women, where the dysovarism leans towards excess, i. e., the flow is too frequent or too heavy, or both. No. 40, *Mamma-Pituitary Co.* (*Harrower*), is used in older women, especially those who are

at "the change" and those who have fibroids. The dosage of either of the above is as follows: One t. i. d., a. c., double three days before and during menses, omit for one week. Repeat.

Ovarian Poisoning. Still one more feature of dysovarism must be mentioned: As we have learned, there is a condition which has been called ovarian poisoning and which results from perversion of the function of the ovarian cells, usually associated with structural changes such as the development of tumors, etc. This dysovarism is far more serious than any of the functional conditions mentioned previously; and while the ultimate successful treatment calls for the surgical removal of the abnormal tissue, it may be that there is a serious adrenal depletion as a result of the toxemia as well as the series of difficulties which are due to ovarian insufficiency. In other words, in those cases where the manifestations of ovarian hypofunction are marked and they are associated with the syndrome of adrenal insufficiency, which includes marked fatigability, low blood pressure and generally reduced cell chemistry, it may be advisable to combine adrenal support with the organotherapeutic regulation of the ovarian difficulty, and for cases of this character the formula No. 79, *Adreno-Ovarian Co.* (*Harrower*), may be advisable. The dose and method of administration are quite similar to the thyro-ovarian preparation already discussed.

Conclusions About Functional Ovarian Disorders. The following conclusions seem to the writer to be both logical and worthy of repeated emphasis:

1. It is accepted that the ovarian function involves the production of one or more internal secretions.

2. Ovarian function is influenced directly and indirectly by the other endocrine glands and it in turn exerts an influence upon the endocrine glands.

3. The thyroid encourages and favors ovarian activity —the cretin does not develop sexually and acquired hypothyroidism usually means ovarian insufficiency.

4. On the other hand, hypo-ovarism, especially at the menopause, favors hypothyroidism—myxedema is more common in women, and nine out of ten cases occur in the decade from 40 to 50.

5. The pituitary is related to ovarian disorders—hypopituitarism causes functional as well as organic sex dystrophies. The Froehlich syndrome includes amenorrhea, obesity and atrophy of the sex organs.

6. Also in functional ovarian insufficiencies other glands may attempt to "help out" vicariously, causing goitre or pituitary headache as the case may be.

7. The intimacy of these glands predicates pluriglandular difficulties when one of them happens to be affected.

8. Amenorrhea or dysmenorrhea—delayed, lessened or difficult menses as well as sterility and asexualism—in a word, hypo-ovarism, is never an ovarian disorder pure and simple. Dalché, of Paris, advises thyroid in all cases needing ovarian therapy (save only in hyperthyroidism).

9. Conclusion: Ovarian dysfunction usually includes thyroid and pituitary dystrophies as well, either as cause or effect. The opposite is equally true. If organotherapy is advisable—and it is—pluriglandular therapy is more likely to reach a pluriglandular disorder than corpus luteum or ovary alone.

This in brief is why *Thyro-Ovarian Co.* (*Harrower*)—a combination of corpus luteum, ovarian substance, thyroid and total pituitary gland in proper proportion—is superior to corpus luteum or ovarian substance alone.

SECTION V. CHAPTER 6

THE PITUITARY FACTOR IN DYSOVARISM

In the previous chapters there have been occasional hints of the influence that the pituitary gland plays in ovarian dysfunction, and this aspect of the subject is so important that it seems well to reiterate these briefly stated facts and supplement them with other information to add emphasis to a very important and usually overlooked subject.

The *Hypophysis Cerebri,* or pituitary gland, is still quite a mysterious organ, and a majority of the profession do not pay much attention to it at all. It is known, in a sort of subconscious way, that there is such an organ, and that it may cause giantism or dwarfism, and that sometimes it may be the seat of a tumor, which causes blindness or intracranial trouble.

Ordinarily, the pituitary is not credited with being much concerned with the "every-day" troubles which come up in the routine of the general practitioner; yet it is an important part of the endocrine system, and a factor in the regulation of any dissimilar functions.

The Pituitary-Gonad Relation. We know that the pituitary gland has much to do with gonad function, for the Froehlich syndrome, or *dystrophia adiposo-genitalis,* is essentially the result of hypopituitarism. Therefore, we may presume that a part of the duties devolving on the pituitary are the initiation or maintenance of sex gland development and activity and, too, that asexualism and hypo-ovarism may have a pituitary element also.

There is a strange relationship between the glands of internal secretion, which causes many of them to assist one another under certain conditions of disability. Perhaps the best known of these vicarious interventions is the faculty possessed by the thyroid of changing its functional routine in order to "help out" the conditions due to ovarian insufficiency. Recall, for example, the comparative frequency of thyroid enlargement at puberty when ovarian activity is beginning, and especially the tendency to goitre in young girls whose menstrual functions are not properly initiated. Again, thyroid changes are not uncommon early in pregnancy, and one of the accepted reasons is the fact that during pregnancy the ovarian functions are largely in abeyance and, rightly or wrongly, the thyroid may be attempting to render uncalled for assistance.

In like manner, the pituitary gland may feel itself called upon to increase its service to the organism under similar circumstances, for we have seen that both the thyroid and the pituitary are known factors in the establishment and regulation of ovarian function. In such an event, the pituitary may become engorged or hyperemic and thus may enlarge itself temporarily in order to accomplish the larger service demanded of it, and since the pituitary is fitted into a bony cup (the *sella turcica*) at the base of the skull, its enlargement, no matter if only slight, may cause an annoying pressure headache. As soon as pituitary or pituitary and ovarian feeding is instituted, or as soon as the ovarian function is reëstablished, the necessity for this pituitary enlargement or engorgement is removed and the headache ceases.

"Pituitary headache," then, is not an unusual accompaniment of ovarian difficulties, especially during the day or days just prior to menstruation, particularly if delayed or abnormal, and its treatment consists in reducing the necessity for this vicarious activity by suitable organotherapy. This explains why *Thyro-Ovarian Co.* (*Harrower*)—corpus luteum and ovarian substance plus suitable small doses of

thyroid *and total pituitary gland*—is more effective in amenorrhea, dysmenorrhea and the neuroses of hypo-ovarism than single gland medication alone. It also explains its efficiency in controlling this type of headache which we will now proceed to enlarge upon a little further.

Pituitary Headaches. In the April, 1921, number of *Southern Medicine and Surgery,* Hodges writes briefly and pointedly on the subject of pituitary cases exhibiting headaches. He calls attention, first, to the symptoms which these patients display. Whether apparently well-developed or poorly nourished, they usually show signs of depression, either physical or mental. They are easily exhausted from effort or exercise, are likely to be forgetful and mentally sluggish. Occasionally, they yawn rather continuously and feel sleepy or "dopey," are without initiative, and inclined to be irritable.

Children suffering from this condition are likely to be "backward" and will probably manifest deficient moral qualities.

These patients sometimes exhibit too much or too little growth of hair over the body, or irregular distribution of the same. In the male there is a curious manifestation of female characteristics, and *vice versa* in the female. The bones also show changes, and are either long or broad, depending upon the age when the metabolism was disturbed. There may be obesity, constipation, and, in women, amenorrhea.

Cases where this "headache" is present manifest many of the signs mentioned but the cephalalgia is the predominating characteristic, and, as Hodges says, "this symptom is really the sentinel to give the alarm in the approaching or complete dysfunction of the pituitary gland. Great importance should be attached to it, for appropriate pituitary therapy at this time, carefully followed, obtains the most satisfactory results."

He calls attention to the pluriglandular aspect of the disorder in the following words: "In studying these cases it is always wise to observe carefully whether or not there may be other glands involved at the same time, for some of these may be stimulators of the pituitary function, or may be acting independently, or in association with the dysfunction of the pituitary. It is hoped that practitioners, by noting these facts, may be enabled to diagnose some hitherto obscure headaches, and especially to recognize this symptom as the precursor of other developments that may

follow; for the important point is that early recognition of pituitary disease, of which this 'headache' symptom is usually the first signal of danger, is the only scientific and successful guarantee for its probable remedial relief."

Clinical Experiences: I have had enough clinical returns from the application of the foregoing suggestions to establish very decidedly the therapeutic possibilities in this type of headache, and to connect the subject incontrovertibly with the ovarian functions. I recall a case of obesity, referred to by me for treatment to a local physician. The associated headache, ovarian disorder and other findings prompted an organotherapy which not merely *cured* a headache of years' standing, but in six or seven months favored a loss of *eighty pounds of superfluous adeps.*

Again, I was told at our last meeting of the California State Society (at Coronado, May, 1921) of a woman who had had a headache *for ten years.* Not a tendency to headache, or even frequent headaches, but an unending, uncontrollable headache. It was found to be aggravated in connection with a disturbed ovarian function, evidently originated in relation to a dysovarism years before and, scientifically or unscientifically, the patient was given *Thyro-Ovarian Co.* (*Harrower*) for 3 or 4 months and was cured—not merely benefited—and for many months she has had no headache at all.

SECTION V. CHAPTER 7

ASEXUALISM AND STERILITY IN WOMEN

Sterility and asexualism in women are very much more common than some may believe. While these two conditions need not necessarily be associated with one another, they may be given brief consideration together. Provided organic elements in the former and psychic elements in the latter can be ruled out, it is very probable that the whole trouble is of an endocrine nature. The former condition usually is borne for years in silence, and the latter often seems too delicate a matter to be taken up with a physician. This subject is none the less of considerable clinical importance and, naturally, is a complex problem. At the close of an interesting paper by Novak (*Jour. A. M. A.*, Aug. 5, 1918), this writer makes the following pertinent statement:

"The reason for the failure of this method of attacking the problem [dilatation or local interference] lies in the fact that the sterility is most likely due to a physiologic defect in the endometrium, that is, the absence of some factor essential to the implantation of the ovum. Here, again, we hark back to disorders of the internal secretory system as the ultimate cause. This, after all, is the conviction borne in on anyone who studies this general problem, whether or not he be a ductless gland enthusiast or 'faddist'—the conviction that the day will come when these very numerous cases of primary amenorrhea, primary dysmenorrhea and sterility, which are associated with uterine hypoplasia, will be successfully treated by correcting the endocrinopathy responsible for the uterine defect."

The Endocrine Causes. For the moment we are concerned chiefly with one aspect only—the endocrine aspect—and the remarks that have been made elsewhere (see "The Hormones in Impotence") apply with just as much force to either sex. The adrenal glands exert the same influence upon general muscular tone in the male as in the female; and the adrenal cortex is just as responsible for its share in ovarian development as for testicular. The essential influence of the thyroid is identical in both sexes, and all that has been said in the chapter referred to about the pituitary aspect of impotence applies with equal force to both asexualism and sterility. It is even believed, from clinical experience, that spermin is an excellent ovarian stimulant—largely, it is presumed, because of its known affinity for the reproductive cells and because of the fact that it stimulates muscular tone and that subtle something known as "dynamos", irrespective of sex.

Thyroid insufficiency is known to have caused sterility and, too, thyroid therapy is known to have cured this disorder many times; hence, the thyroid aspects of the case are worthy of consideration, and my Thyroid Function Test very properly may be used to determine whether the patient has a well-defined degree of thyroid apathy or not. It is well known, and there are plenty of references in the literature to indicate it, that the thyroid stimulates the ovaries, and Oliver T. Osborne, of Yale, has stated that the thyroid gland is virtually an associate ovary, so intimate are the two organs in their correlation of function. We have found that amenorrhea and asexualism are common in hypothyroidism, and that thyroid extract in conjunction with more direct organotherapy renders it very much more efficient.

Hence, a part of the treatment of a sterility in which there is a thyroid factor obviously is thyroid therapy.

The Pituitary Basis of Sterility. It will be recalled that the pituitary gland, as a part of its widespread influence upon the body, has a control over the development and functioning of the sex glands. The typical case of hypopituitarism, or Fröhlich's syndrome, involves not merely amenorrhea but complete ovarian insufficiency with even atrophy, not merely of the ovaries themselves, but the connected adnexa. Infantilism invariably involves the other endocrine glands, especially the thyroid and the pituitary; and organotherapy is the only hope in the treatment of conditions like this. When they are functional or acquired, the chances naturally are very much better than when they have been present since childhood and there has never been any real development of these organs, although even in such cases results show that it is well worth trying.

An Effective Ovarian Stimulant. Pluriglandular therapy, then, would seem to be the most rational method of treating functional sterility as well as asexualism. The combination of thyroid, pituitary and ovarian substances, as represented by *Thyro-Ovarian Co.* (*Harrower*), not merely has served to regulate the abnormal menses and modify the neurotic and psychic manifestations so common in these individuals, but actually has cured sterility in many cases. Dozens of reports have come to me either personally, by telephone, or by letter, of cases in which sterility of years' standing has been changed to fecundity after as short a period as three months, and practically all of those cases discovered that there were changes in their sex manifestations and menstruation prior to the actual impregnation. In other words, these results lend still further emphasis to the necessity of applying organotherapy in functional cases and expecting results in those cases in which the fundamental cause is a dyscrinism.

The following letter received from a prominent gynecologist is of passing interest: "I was very much interested to have one of my old patients report a few days ago that she was 4½ months pregnant. She originally consulted me last spring for sterility, having been married two years. I first had her on lutein for a number of months with no result. She is a strong, healthy woman in every way and there was no apparent reason why she should not conceive. Shortly before my departure for France in July, I put her on your *Thyro-Ovarian Co.* with the happy result that she

became pregnant in September and is now under my care for confinement. I am quite sure that the gland stimulus she received was the important factor in bringing about the desired condition."

Reinforcing Thyro-Ovarian Therapy. In the experimental work done in this laboratory in connection with the development of the *Gonad Co.* (*Harrower*) mentioned in Section V, Ch. 7, an effort was made to develop simultaneously a similar formula for those cases among women of a more severe character that might not respond to the usual Thyro-Ovarian combination. A modification of this latter formula was made by adding a generous dose of anterior pituitary substance and of spermin, and the resulting formula, known now as *Gonad-Ovarian Co.* (*Harrower*), was used in a number of serious cases, as, for example, a case of ovarian insufficiency in which the menses had been absent for six years, a woman who had been barren for thirteen years, and a very unusual case of infantilism in whom a psychosis complicated matters. All three of these seriously difficult cases responded satisfactorily to this formula, and since those experimental days of previous years, many hundreds of cases of disorderd endocrine function, involving especially the sex and reproductive capacity, have been treated in this manner with a sufficiently large average of success to be of great encouragement both to myself and to many scores of physicians who have seen fit to write me in enthusiastic terms.

Rule Out Coincidental Causes. As in the treatment of impotence in the male, extraordinary care must be given to the preliminary diagnostic work in the treatment of asexualism, and especially sterility, in the female. A careful analysis of all the conditions present must be made first. When the examination indicates that the woman is apparently normal, but perhaps functionally and slightly anatomically asexual—with a smaller uterus than normal and, perhaps, some evidence of infantilism—we have an opportunity to apply organotherapy with good prospects of success. However, organotherapy is not effective if a woman has had a specific infection of the Fallopian tubes and their lumina have been occluded, for here the sterility is purely mechanical. Again, if the woman is luetic and consequently is subject to frequent miscarriages, naturally the syphilis must be remedied before normal conditions can be reëstablished, which will allow a pregnancy to run to full term. A mechanical factor in the uterus and especially the endome-

trium, which may prevent impregnation or the nesting of the impregnated ovum and its development, is on a par with the mechanical occlusion of the tubes already mentioned. Under such circumstances organotherapy is foredoomed to failure, and, obviously, causes of this kind must be ruled out first. Some other factors which may militate against our success in the treatment of this condition deserve mention, even though briefly. An infection of the vaginal tract which causes an abnormally acid secretion must be remedied before an associated hypo-ovarism, or dyscrinism involving the ovaries and other associated glands, is treated; for in such cases while the organotherapy may be indicated and, indeed may be efficacious, this chemical factor lessens the chances of the results desired.

The Influence of Organotherapy on the Libido. It has been observed many times, clinically, that ovarian therapy stimulates the ovaries to a better menstrual function, and it is believed that, with this capacity of facilitating a more normal menstrual service to the organism, the other functions of the ovaries are simultaneously encouraged. I have repeatedly seen cases of ovarian insufficiency, in which amenorrhea was the rule, recover also from two other usually associated manifestations—asexualism, or a lessened or lost sex capacity, and sterility. Sexual apathy, or lack of libido, may be a purely endocrine proposition and deserves consideration and treatment from this standpoint. We have seen, for instance, that in myxedema (hypothyroidism), Fröhlich's *dystrophia adiposo-genitalis* (hypopituitarism) this reaction is likely to be lost, and also that it may be lessened, almost entirely by ovarian insufficiency; hence, a treatment embodying these three principles, added to advice in regard to fundamentals, is likely to be efficacious and indeed has been many times, and the use of preparations of the character under discussion here offers better possibilities of success than any other measure that I know of.

This brings us to a point of diagnostic value which amplifies the position outlined in Section II, Chapter 6, "Diagnostic Organotherapy": If a woman has a normal menstruation and a normal sex reaction and is still sterile, the chances are that the obstacle is an anatomical one, and not likely to be amenable to organotherapy.

If, on the other hand, there is other evidence (besides the sterility) of ovarian insufficiency as manifested by amenorrhea and asexualism, the chances for clinical results are better, because it is likely under such circumstances that

the ovarian endocrine complex, as a whole, is deficient; in other words, that there is pluriglandular insufficiency, involving not merely the ovaries, but those glands which encourage and help to maintain the service to the body.

In spite of the inherent difficulties in considering and treating this class of cases, and especially the many opportunities for failure resulting from the ignoring of overlooked factors of the character already mentioned with emphasis, I have seen personally enough individuals with light in their eyes and enthusiasm in their tone to be converted for all time to the real possibilities of this method. I have read scores of reports confirming my attitude and I have more confidence in this particular present-day method of treating hypogonadism than I ever had before I made myself acquainted with the importance of the relations of the endocrine glands and the control that many of them exert upon one another.

Routine Treatment Outlined. My method in treating these cases of sterility and asexualism is first to assure myself that there are no extraneous factors of a non-endocrine character. All of the points already mentioned must be carefully gone over. The husband must be examined, and only when the case is evidently of an endocrine character is organotherapy indicated.

The formulas known as *Gonad-Ovarian Co.* (*Harrower*) should be given for several weeks and perhaps months, for, naturally, organotherapy in long-standing conditions is in the nature of an educative factor and such measures as this take time. This formula, *Gonad-Ovarian Co.* (*Harrower*) is best given in the cyclic manner referred to in the previous chapter, in the expectation of exerting the utmost influence upon the ovaries at their height of functional activity; consequently, at the onset of menstruation, the preparation may be omitted for several days. I am in the habit of advising a break of ten days commencing at the beginning of the flow; then giving one dose three times a day during the next ten days, and doubling this dose for ten days prior to the expected flow. This is then repeated for at least three or four periods.

In individuals in whom there is no menstruation nor molimen, the same step-ladder method may be followed, the month being divided arbitrarily into three equal parts; and as soon as there is the slightest evidence of discomfort in the nature of a molimen, or ever so small a flow, the remedy is omitted for the short period thereafter and then

pushed; i. e., the dose is doubled, for a week or ten days prior to the expected periodic manifestation which later on may establish itself and serve as an indicator as to when to modify the dosage.

SECTION V. CHAPTER 8

GALACTAGOGUE ORGANOTHERAPY

The appreciation of the factors responsible for the establishing and maintenance of satisfactory lactation is obviously of fundamental importance to human welfare and of much practical value in general practice.

Deficient milk production—agalactia or hypogalactia—is common enough, and aside from the influence it may have upon infant health and mortality, it also has a very definite physiological relation to pelvic disturbances in the mother, for nursing is also a normal factor in ovaro-uterine physiology, and those who will not or cannot nurse their children often have to suffer for it later on.

There are no very well known galactagogue remedies. The administration of plenty of milk and cream and other dietetic care usually constitutes the best that we can do. We feed cotton-seed cakes to our cattle because gossypiin is a recognized galactagogue, yet this principle is rarely used in medicine. Various malt preparations and special foods are recommended, all of which act upon this function indirectly.

Hormone Control of the Mammae. Mammary development and secretion seem to be definitely under the control of hormone influences. The ovarian hormone has been shown to stimulate mammary development. A hormone produced in the fetus itself causes the formation of milk, the placenta also has something tangible to do with this, and finally the absence or removal of these various factors causes a stoppage of this function. With this in mind it should be possible artificially to bring about desired stimulation by some form of organotherapy. With the well-established principle of hormone stimulation in mind, it was natural to try the administration of mammary substance, and some indubitable results have followed this procedure. It is now established that mammary extract is a galactagogue. Some experimental work upon cows, at Cornell University, has

also demonstrated that the pituitary gland contains within it an active galactagogue principle, and a number of records in the literature of agriculture as well as medicine indicate that its use for this purpose is at least feasible.

Further, and most important, the placenta has been found not merely to be an organ of internal secretion but to be a means of artificially increasing a deficient supply of milk. It is interesting to know that quite recently a French scientist, de Kervily, has shown that certain vacuolated cells normally found in the placenta are actually secretory elements and presumably similar to the internal secretory cells of the pancreas, which are found in the islets of Langerhans.

Placenta Substance as a Galactagogue. The original use of this measure seems to be very old, and unquestionably, is based upon the observation that domestic animals, almost without exception, manifest a remarkable and uniform instinct to devour the placenta as soon as it is delivered. It is clear that these animals do not eat the placenta through hunger or instinct to keep the nest clean, for it will be recalled that the cow is herbivorous and has no nest!

Some very practical and interesting experiences were obtained by Dr. Bertha Van Hoosen, of Chicago, who made a number of experiments at the Mary Thompson Hospital (*Woman's Med. Jour.*, Dec., 1916). Thirty grains of desiccated placenta were given daily to a series of cases in six doses an hour apart. The first report was a complaint from the nurses—the patients had so much milk that it was a burden to keep the breasts empty! A case is mentioned in which 16 ounces of milk were removed after the infant had taken all it would. Three others had 6 ounces removed immediately after nursing. A fifth patient had 8 ounces, and a sixth had 4 ounces removed under like circumstances. Generous quantities of superfluous milk were obtained without depriving the child, the only object being to secure comfort for the mother. Tabulated findings indicate that the infants of placenta-fed mothers maintained or increased their birth weight at the end of the second week, whereas comparisons between a large number of treated and untreated indicated that the average loss during the first week was 9½ ounces, whereas in the cases where desiccated placenta was used, the average loss was only 5½ ounces for the first week. During the second week, the average gain was 50 per cent. greater than in the untreated infants, the conclusion being that the "administration of

desiccated placenta produces an early and gradual stimulation of the secretion of milk and no other by-effects."

R. T. Frank, of New York (*Jour. Cancer Research*, 2, 1917), determined that placental extracts "experimentally stimulate the breasts, increasing the area and developing the ducts, acini and nipples." S .W. Bandler, also of New York, includes mammary extract and placental substance among "the valuable opotherapeutic products." (*Endocrinology*, June, 1919.) E. L. Cornell, of Chicago, reports some experiences with the galactagogue influence, especially the indirect effect upon the infants. Of the cases studied, 87 per cent. began to gain on the 4th or 5th days, as against 69 per cent. of those whose mothers did not take the extract. Of the treated cases, 44 per cent. regained the birth weight before leaving the hospital, as against only 24 per cent. of the latter. Very little attention has been paid to statistical studies of this character, and these figures are an additional encouragement to those who have been urging this matter for years.

Much experimental work has been done, and it has been found that preparations of this character not only exert a tonic involuting influence on the postpartum uterus, but according to Ercole Cova, an Italian investigator (*Anna. Ostet. e Gin*, Sept., 1915), placenta extracts may be used therapeutically in the treatment of hypoplastic uterus, for it seems that there is a principle in the placenta that causes growth in the uterus, both during pregnancy and in abnormal infantile cases. This particular phase of organotherapy indeed seems quite promising.

A Pluriglandular Galactagogue Formula. For a number of years, I have been recommending a formula embodying the three glandular preparations mentioned here— mammary substance for its hormone stimulant effect upon the mammary glands, placenta for its indubitable galactagogue effect, and pituitary gland for its possible benefit to milk production and its associated value as a general and uterine tonic. This formula, under the name *Placento-Mammary Co.* (*Harrower*), has been used for some time with quite unusual success when there has been a serious reduction of the amount of milk secreted; but it is more rational as a prophylactic and is recommended as a routine procedure following labor. The initial dose is ten grains at each of three meals daily for ten days or two weeks, thereafter continuing the administration of one dose three times a day for several weeks.

There also seems to be some relation between nursing, the administration of placenta extract, and early menstruation after pregnancy. I recall a recent inquiry from a colleague, who asked if the *Placento-Mammary Co.* prevented menstruation. I was noncommittal in my reply, because I really did not know. I said that it was supposed to favor the establishment of normal postpartum conditions, including the milk supply and uterine involution. I remarked that menstruation during lactation was not normal, and was not surprised to learn the following case report: A 3-para who had had difficulty in nursing her other children, and who has always menstruated five or six weeks after delivery and thereafter fairly regularly, had been given the *Placento-Mammary Co.* to obviate the expected difficulty with the nursing if that were possible. The response was splendid and there was enough milk and to spare, but to the surprise of the patient she did not menstruate for over five months, during all of which period she was satisfactorily nursing her baby.

The Control of Galactorrhea. Some time ago, among the queries received at my office was one asking whether there is anything in organotherapy which could stop the functioning of the mammary glands, the case in question being that of a woman who ever since her first pregnancy had had a continuous flow of milk which could not be stopped either by belladonna or any other means. My reply was more or less as follows: The mammæ are definitely antagonized by the ovaries and *vice versa.* Mammary therapy many times has relieved menorrhagia and pelvic congestion due to ovarian irritability. On the other hand, ovarian feeding is contraindicated during lactation, and, too, the mammary activities are greatest when ovarian function is in abeyance. The excellent thesis of Schil (Nancy, 1912), concerning mammary evolution and function is a comprehensive study of the subject. An abstract of it will be found in my book, "Practical Hormone Therapy," pages 371-3.

Bearing these facts in mind we might properly attempt to antagonize mammary hyperactivity by ovarian feeding or corpus luteum. It is theoretical, for I know of no case in which this method has been tried; but, at least, it is not unreasonable. I would suggest fairly heavy dosage of desiccated ovarian substance for a month or more; and at the same time I would use the usual mechanical pressure by the bandage and atropin as well, giving, say, 1-200 of a grain of atropin sulphate by mouth three times a day.

SECTION V. CHAPTER 9

THE CONTROL OF MENORRHAGIA

Menorrhagia and ovarian irritability are often treated successfully with mammary substance and the therapeutic effects of this unusual preparation indicate that it is "an antiovarian remedy." Some study of the physiology and clinical experiences with mammary extract will be an advantage.

Whether or not the mammary glands are really glands of internal secretion is a moot question. Some say "Yes" and prove it in a fairly intelligible manner, while others say "No"—on general principles! Certain facts indicate, however, that these glands deserve at least to be considered from this viewpoint, for the mammæ are under hormone control and they contain within their structure a substance which remains in the desiccated substance and which, when used as a remedy, exerts a definite action (homostimulant) upon the mammæ themselves, as well as upon other remote organs.

The Hormone Control of the Mammary Glands. A number of common experiences remind us of the hormone relations of the mammæ: It is a well-established fact that the operation of spaying dairy cows at the time of their greatest flow of milk has a distinct lengthening influence upon the lacteal period. Additional emphasis is lent by the fact that the function of ovulation is retarded and sometimes entirely stopped during prolonged lactation, presumably because in this stage of mammary activity ovarian activity is antagonized in a greater or less degree, due, as some will have it, to an associated increased elaboration of the internal secretion of the mammary glands. It is also well known that the supply of milk is considerably lessened soon after a new conception takes place.

Still another aspect to this subject is worthy of passing comment: I have frequently noticed a relationship between very large mammary development and scanty menstruation. In a paper entitled "Mammary Therapeutics; The Mammæ as Glands of Internal Secretion" (*Woman's Med. Jour.*, Mar., 1914), I called attention to this, and it was remarked that while this is by no means always the case, it points at least to an antagonism between the mammæ and ovaries. Late in 1918, Oliver T. Osborne, of Yale University, wrote, "Girls

with very large mammary glands may have long periods of amenorrhea without pregnancy, or they have very irregular or scanty menstruation."

Most of these findings indicate that the breasts are related in some way to hormone influences, i. e., they may exert some control through an internal secretion upon the ovaries or other organs. Further proof of this activity will be forthcoming, for, as will be seen shortly, this antagonism is put to good use in therapeutics.

Origin and Clinical Value. Numerous references to the use of mammary extracts show conclusively that they have caused decided therapeutic effects, and at the same time emphasize the importance of what still must be called a much neglected field of therapeutics. In fact this is getting to be a well-established part of organotherapy, despite denials which still are heard occasionally. The truth is, that *mammary substance is one of our best measures for antagonizing ovarian activity and lessening functional congestion in the pelvis.*

Mammary extract is produced from the carefully desiccated parenchyma of the udders of cows, goats or ewes, and is prepared in dry form with the precautions customary in the manufacture of effective organotherapeutic preparations; and whatever the principle may be that is the cause of the therapeutic activity of this extract, it is evidently not destroyed when passing through the stomach. Incidentally, much work has been done with soluble mammary extracts given hypodermically, but they have been virtually discarded in clinical practice because of the local pain and induration which so often follows such injections.

The Control of Menorrhagia. Because of the antagonism between the mammæ and the ovaries, it was natural that mammary extract should be used in the attempt to overcome the results of excessive ovarian activity. Among the conditions which have been classed under this head are menorrhagia with increased uterine congestion, uterine hypertrophy and fibroid degeneration, as well as certain conditions in which there is an increased degree of functional ovarian activity, including nymphomania, etc.

A number of investigators have used this method to produce uterine depletion and to control hemorrhages shown to be due to functional causes as distinguished from those of organic origin, such as the presence of foreign bodies in the uterus, polypi, placental remains, cancer, etc. Osborne stated very recently that "profuse menstruation in girls

. . . may be prevented by the administration of mammary substance." In another place, the same writer says, "A profuse or too frequent menstruation, where there is no pathological excuse, especially in young girls, may be corrected by feeding mammary extracts."

Pochon has used mammary substance and recommends it for its decided anti-hemorrhagic influence (however, it is not a styptic by any means) and calls attention to the fact that while mammary extract tends to cause uterine depletion, ovarian extracts have an entire opposite tendency, causing an increased uterine blood supply. Battuaud indicates that this form of medication has proved valuable in the control of menorrhagia in young girls, just as it has been found serviceable in metrorrhagia of the climacteric. Congestive conditions of the ovary resulting from inflamation of the adnexa and other causes may be reduced in this manner, although, of course, the influence is more mechanical—i. e., decongestion is brought about in a chemical way and there is no particular action on the infective process. In other words, mammary extract is a valuable adjunct to treatment. Dalché, Jayle, Pozzi and other French gynecologists have expressed themselves freely as convinced of the efficacy of this method. The advantage of this depletion is obvious in pelvic congestion of varied origin. It has been used in severe pelvic pain due to infection (and consequent congestion), and even in uterine cancer with constant oozing where results have been so good—stoppage of all flow and reduction of the bad odor—that the patient has anticipated a cure, though, of course, this is not possible. Luncz, in his interesting monograph, has gathered a number of reports of benign cases in which mammary opotherapy caused an entire cessation of severe uterine hemorrhage in persons of widely varying age.

Other writers have gone further, among them Forgue and Massabuan, who, besides demonstrating clinically the anti-hemorrhagic action of this preparation, have shown experimentally that at the menopause there frequently is an obvious increase in the corpora lutea with hypertrophy of these cells. They presume that the hemorrhages so common at this time may be due to two causes: Temporary increased production of the luteal hormone, and an associated decrease in the production of its antagonist—the mammary hormone—resulting, of course, from the usual retrogressive changes expected in the mammæ at this period. This harmonizes entirely with the facts previously

collated here, and is further evidence of the soundness of the position that I have taken for years and established to my own personal satisfaction, i. e., that *this particular anti-hemorrhagic influence of mammary substance is indeed a reality in many cases.*

Preparations Containing Mammary Substance. Among the formulas made in The Harrower Laboratory are three containing mammary gland. The first of these, No. 3, *Placento-Mammary Co.* (*Harrower*), is used chiefly as a galactagogue where the homostimulant effect of the remedy supplements the more active effect of desiccated placenta. The subject is given full consideration in Chapter 8 of this Section.

Another mammary combination, No. 38, *Mamma-Ovary Co.* (*Harrower*), is used in menstrual difficulties of an ovarian character which lean toward an excessive flow. This class of cases is hardly to be called menorrhagia, since the flow usually is not particularly serious. In these cases, ordinarily occurring in girls and quite young women (in contradistinction to the real menorrhagia of older women, especially at the menopause) the flow lasts six, seven or more days and may recur at shorter intervals than is normal. Here there is not so much a condition of ovarian irritability or excess as a dysovarism which is accompanied by pelvic congestion and the minor form of menorrhagia just mentioned. Because there is a decided dysfunction of the ovaries, the mammary substance is combined with a thyro-ovarian combination; and despite the known relations of these glands, the body seems to be able to use the differing stimuli simultaneously. In cases of dysovarism which tend toward a prolonged or too frequent flow, this formula may be superior to the more frequently used *Thyro-Ovarian Co.* (*Harrower*), which is considered elsewhere.

Still another formula of this type deserves to be mentioned: No. 40, *Mamma-Pituitary Co.* (*Harrower*), used for the control of uterine bleeding, whether postpartum, climacteric, fibroid, or even in cancer. Made originally for a prominent Oakland obstetrician, this formula contains a suitable dose of Bonjean's ergotin, which clinical experience has shown sensitizes the uterus so that the effect of the associated remedies is most direct. This is a rational as well as an effective uterine styptic, exerting its influence from within, gradually and very often permanently. Its value is broadened by the utero-tonic influence of the added pituitary gland (total).

The Influence on Fibroid Tumors. More than 20 years ago Robert Bell, of London, discovered that mammary extract exerted an influence upon the uterine fibromata which caused a reduction or cure of the menorrhagia and a recession in their size. Feodoroff, of Petrograd, wrote many reports on the subject and enthusiastically advocates this treatment. As a matter of fact, reports enumerating more than a hundred cases in all might be collected from the literature extolling mammary extract as a curative remedy for this condition. I have not had much personal success in half a dozen cases personally treated, but I have seen cases that responded to the same method, while a number of physicians have written to me or told of indubitably good results. I prefer not to urge mammary preparations as a means of remedying fibroids but rather to recommend their use in the functional conditions such as show themselves in menorrhagia, etc., but I will not deny that there are possibilities that if this treatment, preferably perhaps the *Mamma-Pituitary Co.* (*Harrower*), is used to control the hemorrhagic feature of the fibroid syndrome, besides the expected benefit to the menorrhagia there may be a very pleasing reduction in the size of the tumor. Briggs, of Sacramento, is a more recent writer on this subject (*Calif. State Jour. Med.*, Sept., 1917.) He reports his experiences which were quite encouraging and believes that the mammary hormone probably antagonizes the uterine stromal hormone, thereby modifying or preventing excessive hyperemia and thus controlling menorrhagia and the local nutrition of the uterine tissue (fibroid). The effective dosage depends on the degree of hyperovarism. I learn from a physician in Mexico that the above formula has been used by him for six months in a woman with an "inoperable fibroid," with hemorrhages, malnutrition, and a heart which precluded surgery. He writes: "The excessive flow has been entirely controlled, the patient is better in every way and the fibroid is reduced fully one half."

Interesting Clinical Experience. A physician in Oregon was good enough to write me about his experiences with this treatment, and a part of his letter follows. "The first, an unmarried woman, age 45, has a large tumor of the right ovary. She is entering the menopause with excessive floodings. Hemorrhages lasting (when she came to me) for over three weeks; pallor extreme; wild expression in eyes; face tense and drawn. Patient perpetually exhausted. After local examination, bimanual, no instruments at-

tempted, put her in bed again ten days. She flooded for eight days. She had a lapse of only two weeks (longest period) for three months during hemorrhages. Put patient on *Mamma-Pituitary Co.* (*Harrower*), as indicated. Within first week she showed marked signs of improvement. The next period came in four weeks and she flowed four days and stopped—that has been the report for another two months. She is feeling like a different human and her friends see such a marked improvement they wonder what is happening. They saw great changes within the first week of administration and marvelled.

"The second woman, age 38, married fifteen years, sterile, has a uterine fibroid. Until recently she had considered herself a 'well woman' but complained of excessive backache through the scapular and mid-dorsal regions. Examination revealed a fibroid the size of a large infant's head wedged into the pelvis, with a hard, prominent ball-shaped mass protruding above the brim of the pelvis; easily palpable through the abdominal wall. She flows excessively, monthly, 7-8 days, with heavy clots and is very weak and pale following each period. First month after administration of *Mamma-Pituitary Co.* she flowed four days and the flow was and is in strings and shredded instead of in large clots. She felt stronger and able to do housework and washing, which she did. Examination shows no special change intra-vaginally, *but through abdominal wall a marked change.* The 'ball' effect has softened and spread out; a most pronounced example of a breaking-down and absorbing of false tissue. Patient is passing through second period of menstruation since dosage began; the change is most noticeable to her own palpation; and she is most conscious of a general improvement."

The Administration of Mammary Products. It will be recalled that a step-ladder method is recommended for the use of ovarian preparations (see Chapter 5 of this Section), and I will advise a modification of it for the use of either of the formulas, Nos. 38 and 40. The average dose is five grains, occasionally ten, three times a day, ordinarily just before meals. This is increased a few days before the expected flow and the dose *continued through the entire flow,* it being omitted thereafter for perhaps a week or longer, depending upon circumstances, and repeated for several months, always pushing the dosage just prior to and during the menstrual flow, and resting for a while immediately it is ended.

SECTION V. CHAPTER 10

A ROUTINE TREATMENT OF HYPERTHYROIDISM

Hyperthyroidism, or, as it is sometimes termed, thyrotoxicosis, is one of the principal forms of thyroid dyscrasia, and, as stated elsewhere in this book, is at once the best-known and the most complex of all the functional thyroid diseases. It is also one of the most serious problems of medicine, for a study of the very extensive literature on the subject rapidly brings us to the conclusion that there is much diversity of opinion in regard to the origin, clinical relations, and, particularly, the treatment of this disease.*

The Essential Etiology. It is still claimed by many that the origin of hyperthyroidism is a mystery. To my mind, however, toxemia—chemical, bacterial, endocrine or emotional—is the real cause. It is, however, the complicated associated factors which constitute the principal sources of difficulty. The complexity of this disease and the frequent stubbornness of its response to treatment—whether medical or surgical—makes the study of the subject so much the more important. The fact that the prognosis is not good, and that radical cures are by no means the rule, should be an incentive to the rank and file of the profession—who, by the way, encounter by far the majority of cases of hyperthyroidism—to study this subject still harder.

In this syndrome the thyroid gland is unusually active, with or without a marked increase in its size. "Exopthalmic goitre" is the term most commonly given to this condition, though an excessive thyroid secretion may be present without the exophthalmos, and, rarely, the exophthalmos may be in evidence without the goitre. (Let me here place on record that I am not in favor of identifying hyperthyroidism with the name of some physician, which leads to some confusion.) Parry (who originally discovered the syndrome in 1786), Flajani, Graves, and von Basedow have each in turn had their names classed with the syndrome, the last two names being those most closely linked with it.

* The first (January 1921) issue of *Harrower's Monographs on the Internal Secretions* is on this subject and is entitled "Hyperthyroidism: Medical Aspects." It contains much interesting information collected from many scattered sources, conveniently arranged and fully bibliographed. 120 pages, sewed, price $1.50 postpaid. (The annual subscription for this quarterly publication is $3.00.)

Various Lines of Treatment. Hyperthyroidism, unfortunately is a very common endocrine manifestation, especially in women during the period of ovarian activity. The suggestions in regard to its treatment differ widely. Some advise sedative drugs, others alteratives; still others urge destructive measures such as the X-ray, radium, injections of boiling water, or a solution of quinine and urea hydrochloride. If the thyroid is enlarged, and there are a number of disconcerting symptoms, the surgeon removes as much of it as he dares. The medical treatment consists largely in rest, sedative drugs like the bromides, hydrobromide of quinine, chloretone—plus an expectant attitude! A third method of treatment consists of an attempt to find the cause and control it while simultaneously neutralizing, as may be within our power, the erratic glandular dysfunction and its results. This last procedure will be given further consideration here as it has become my routine in all cases of hyperthyroidism.

Medicine Compared With Surgery. While I am not opposed to surgery, provided medicine has failed and no removable or modifiable underlying causes have been discovered, I am nevertheless most decidedly against the removal of an enlarged thyroid gland when the cause of such is ignored and when medical measures have not been applied. The medical treatment as mentioned under the second heading does not fit in with my idea of what should be done, because the attempt is merely to control symptoms; it may be advisable, but only as an adjunct to a better procedure.

The last method of treatment involves three important things which have to be accomplished, viz: (1) the control of toxemia, and especially of its serious cardiac manifestations; (2) the removal of sundry and widely differing causes of thyroid irritability; and (3) the reëstablishment of the deranged chemistry and the restoration of the badly disorganized nutrition. I, in common with a growing number of others, favor a comprehensive routine which will neutralize not merely the thyroid dyshormonism, but simultaneously will care for all forms of toxemia, regulate the diet and alimentary conditions, and control the associated disturbances, whether causative or resultant. Nevertheless, each of the two schools, whose ideas are so widely separated fundamentally, has its adherents who urge their particular viewpoint. The surgeon, on the one hand, cannot see eye-to-eye with his medical colleague, while many

a statement in the literature emphasizes the superiority of the medical as compared with the surgical treatment of hyperthyroidism, taken as a whole.

From my own standpoint I am convinced that many a failure in the treatment of this disease is as often due to the omission of essential procedure as to the selection of "a wrong method." This is particularly true in regard to the various surgical procedures. The greatest satisfaction in the solving of this difficult endocrine problem comes from the studied application *of all the prospectively useful measures,* some of which have been indicated above; and fortunately they are of such a character that most of them may be used together. Rest, diet, hydrotherapy, detoxication, the X-ray, organotherapy, and the use of certain drugs, may all be fitted together and made part of a routine treatment. Then, of course, associated causative elements, as focal infections, emotional factors, and disorders of other endocrine glands, necessarily must have their share of attention in conjunction with the active treatment.

Disturbances in Other Glands. Among "other endocrine disorders" which have a distinct relation to hyperthyroidism may be mentioned those connected with the pancreas, parathyroid glands, pituitary, thymus, gonads, and, most important perhaps of all, the adrenals. I have called attention repeatedly to the frequency of hyperadrenia in hyperthyroidism, and believe that either the factors which irritate the thyroid into excessive activity, or the actual excess of the normal thyroid principle, suffices to stimulate the adrenal glands abnormally, with a resulting irritability, sympatheticotonus, and later, adrenal depletion, with its typical asthenic syndrome. Experimentalists such as Herring and Hoskins have found that thyroid feeding causes a hypertropy of the adrenal glands both in the cortical and medullary portions. Herring's experiments with cats, which were fed on thyroid, showed adrenal hyperplasia, with an increase of the adrenin content. An application of this in practical form is found in the Goetsch test, already referred to, or the injection of adrenalin in supposedly hyperthyroid cases. A further hint of the possible relations between the adrenal glands and the thyroid is the fact that not infrequently in hyperthyroidism there is a pigmentation of the skin just as there is in Addison's disease.

Among the other endocrine glands which are particularly likely to enter into the etiology of hyperthyroidism is *the thymus,* which may be both persistent and enlarged,

thereby adding to the complex what has been called hyperthymism. A number of prominent investigators have found that a goodly percentage of patients suffering from hyperthyroidism have a persistent thymus and that treatment calculated to reduce the thymus (the suitable exposure to the X-ray, perhaps half a dozen times) not merely disposes of the thymus but mitigates the symptoms of the hyperthyroidism very materially. Hence a condition of this kind should be looked for in every case and disposed of when it is found.

Finally, *the ovaries* often are closely related to dysthyroidism, and when one appreciates the close dependence of the thyroid upon the gonads, and especially, the ovaries upon the thyroid, it is clear how any disturbed function of the ovaries may react upon the thyroid sufficiently to derange its normal routine. Personally I do not believe that hyperthyroidism is related to ovarian dysfunction as often as ovarian dysfunction is related to hypothyroidism; but there is a relation, and when there is a disturbance of ovarian function it should be sought for and controlled, and this is usually best accomplished by suitable organotherapy.

Failures in the Treatment of Hyperthyroidism. The greatest source of failure in the treatment of hyperthyroidism lies in ignoring overlooked causes; and this fault is the greater when the treatment planned is to be of such a nature as to be irrevocable. I cannot lay too much emphasis upon the fact that this disorder is not merely an irritability of the thyroid gland, with a corresponding increase in the production of its hormones. As a matter of fact, it is really a manifestation of a much more subtle and deeply-laid disturbance in the functions of the body. As I see it, there are three fundamental causes, any or all of which may be related to the onset of the thyroid irritability. The first of these may consist of various foci of infection, and every case of hyperthyroidism should be very carefully examined from every possible standpoint so as to exclude conditions which would favor the absorption of bacterial poisons into the system. The teeth, tonsils, sinuses, lungs, gall-bladder, intestines, appendix, and pelvis, all should be carefully studied from this standpoint, and if it is believed that there is a condition of focal bacterial toxemia, obviously it must be taken care of, for no treatment, whether surgery of the thyroid or the very best medical regimen—with or without such measures as I have mentioned here—could possibly have any direct influence upon a focal infection. Inciden-

tally, herein lies the error of some surgeons! The thyroid gland is so obviously at the root of the serious sympathetic imbalance that of course it must be removed forthwith, *while the real underlying cause remains* to bring as much trouble later on by irritation of that part of the thyroid which must necessarily be left behind. This is wrong; but my remark does not mean that I am opposed to surgery under certain circumstances, for undoubtedly it is occasionally necessary and decidedly helpful; but I have seen too many post-operative cases to believe that the thyroid is the chief offender. *It is merely the victim of circumstances.*

The emotional aspects of hyperthyroidism, too, are extremely important. Indeed the thyroid function may be unbalanced solely as the result of a mental shock, and, without any question, instability of the nervous system is not merely the result of hyperthyroidism, *but may be the cause of it as well.* This complicates matters very much indeed and explains the necessity for rest and a congenial environment as well as the removal of all factors which might aggravate conditions which act through the medium of the emotions. It also explains the good results that we often secure from a change of circumstances and cessation of all work and worry, in our treatment of these cases.

As we have seen elsewhere and as has been so thoroughly emphasized in the writings of Elliott of London, Cannon of Boston and Léopold Levi of Paris, the emotions exert a specific effect upon the chemistry of the body through the faculty of the adrenal glands to respond to emotional stimuli such as fright, as following an accident; fear; rage or anger; pain, and even worry. All these excite the adrenals and in this manner sensitize or irritate the entire sympathetic mechanism. In such cases, rest and the removal of these emotional tendencies must be a part of the treatment.

Antagonistic Organotherapy. The immediate treatment of hyperthyroidism, in my estimation, centers upon the control of the heart action, and this is accomplished quite satisfactorily by placing the patient at absolute rest in bed in a quiet room, remote from worry and noise. Suitable hydrotherapy may be also helpful. An important remedy in hyperthyroidism is the infundibular principle of the pituitary gland, and injections of a half to one mil. of *Liq. Hypophysis* (*U. S. P.*) seem to exert an antagonistic effect upon some of the underlying dyscrinisms and also to slow the support of the heart.

There are a number of phases of organotherapy that may be used to control the manifestations of hyperthyroidism, and let it be said that this is a very much more difficult proposition than the treatment of hypothyroidism. It is obvious that all of these patients are in a state of severe cellular irritability, and the sympathetic nervous system in particular is decidedly "on edge." The condition is technically known as "sympathetico-tonus," and is the opposite of the condition known as "vagotonia."

In all conditions of sympathetic irritability, the adrenal glands usually are hyperactive, and I do not believe that a case of thyroid excess exists that is not complicated by an associated hyperadrenia. If this is so, the use of the normal antagonist to the adrenal function—the pancreas—should contain within it possibilities of distinct value, and, in fact, a number of reports in the literature and many personal experiences convince me that pancreas substance (not pancreatin) has a definite sedative value in this disease.

A number of authorities have recommended pluriglandular combinations, among them André Crotti of Columbus, (who, by the way, also emphasized the frequency with which there is an ovarian aspect to hyperthyroidism). His formula consists of equal parts (three quarters of a grain) of desiccated adrenal, pituitary, pancreas and ovary—*total gland* in each instance. Several French writers recommend adrenal and pituitary, and there is a large amount of literature from which it may be gathered that dysovarism is so commonly associated with hyperthyroidism that it may be the sole causative element, and that the treatment of ovarian dysfunction may suffice to cause a marked change for the better in the thyroid manifestations.

I have been using and recommending a pluriglandular formula containing the same ingredients as those suggested by Crotti but in somewhat different proportions. This formula is called *Pancreas Co.* (*Harrower*), and each 5-grain dose consists of one half grain each of total adrenal and pituitary substance, one grain of ovary and three grains of desiccated pancreas gland. The first two may have some subtle influence upon causative elements of an endocrine character (several writers hint at this), but the chief reason for their inclusion in the formula is because of their supportive influence upon the heart, while the ovarian substance exerts its usual effect, and the generous dose of pancreas is a physiological, sympathetic sedative. This

formula has been used in quite a number of cases, and its symptomatic value in many instances seems to cause just the kind of steadying needed in the cellular excitement of Graves's disease and allied disorders.

It will be recalled that the pancreas and adrenal glands are direct antagonists, and one may wonder why these antagonists are given together. I cannot answer this as easily as the question may be asked. It is possible that the adrenal gland, which includes the adrenal cortex, the so-called interrenal organ, has some influence in cases of this character, for certainly this gland has a great deal to do with the regulation of the gonads and the thyroid. Looking at it from another standpoint, it is possible that the adrenal element in this formula is useful purely for its effect upon the heart. At all events, the combination seems to be superior to the use of either adrenal substance or pituitary alone, or the use of pancreas substance alone.

I am prompted to quote several paragraphs from a letter received personally from a graduate nurse who had been developing an annoying hyperthyroidism which resisted several efforts at treatment, and who was referred to me by a relative and treated at somewhat long range.

"My markedly improved physical condition is a matter of considerable comment. The folks at the hospital got quite excited about it and asked many questions as to what you had been giving me, how long I had been under treatment, dosage effect, etc. Dr. ——— was especially interested as he had previously told me that my condition was rather serious and that you probably had nothing suited to my particular case. I told him how various symptoms had been fixed up and he thought that was well enough but that results could not be all that were desired unless so proven by the metabolism test. They gave me the test free this time and said they wanted it as an experiment. I thought you might also be interested, as the B. M. R. before the beginning of the treatment was 20 per cent. above normal and the last one, 5 per cent below." And in this case, while the metabolism was not nearly as markedly increased as I have seen it, there were the usual nervous symptoms, cardiac irritability and rapid pulse, digestive disturbances and noticeable loss in weight, all of which apparently were regulated by the organotherapy that is routinely recommended.

The Associated Treatment. While this chapter concerns essentially the endocrine side of the subject, associated

treatment is so important that it must receive attention also; in fact, a successful outcome in hyperthyroidism is the result of the appreciation of all of the involved factors and their simultaneous treatment. Obviously, sources of toxemia must be removed, and the colon is the great cause of offense. My routine treatment in such cases consists in persistent colonic flushing, oil enemas, and intelligent measures calculated to unload the colon and loosen accumulated concretions, especially at the angles of this organ. Too much attention cannot be paid to colon hygiene in hyperthyroidism. In this connection, I must refer to the frequent association of hyperthyroidism with mucous colitis, and it may be well to give consideration to the suggestions made in the chapter on that subject. After the colon is fairly well cleaned out, regulate the diet so that it will remain as sweet as possible, using the *bacillus bulgaricus* in cultures, tablets, or cultured milk. If necessary, recommend suitable intestinal antiseptics, avoiding, however, all preparations containing iodin. Finally, since the hyperthyroid individual is burning up more of herself and her food than she can afford to lose, a generous and nutritious diet must be given and special efforts taken to ensure its assimilation. Incidentally, one of the reasons why the pancreas gland is a useful remedy in hyperthyroidism is due to the fact that it also encourages the pancreas function, which concerns digestion (external secretion) and carbohydrate metabolism (internal secretion).

Increasing the Alkaline Reserve. All of these factors mentioned must be considered in every case of hyperthyroidism and suitable indicated treatment be carried out. Yet there is still one other thing that needs to be done almost invariably. Hyperthyroidism is very commonly associated with demineralization. The underlying causative toxic condition, besides irritating the thyroid, is robbing the body of its alkali mineral reserve in the manner outlined quite fully in the chapter on Remineralization; hence, to all of the treatment just suggested should be added the alkali mineral salts, such as the body requires, in generous quantities to neutralize the excessive tendency to acidosis or acidemia so common in these cases.

To recapitulate: The treatment of hyperthyroidism should consist (1) in a search for causes and their removal as completely as may be possible; (2) the support of the heart and antagonizing of the sympathetic irritability, preferably by the use of the pluriglandular compound *Pan-*

creas Co. mentioned above (four to six 5-grain doses a day, more if it seems advisable); (3) neutralization of the tendency to acidemia and the building-up of the mineral reserve may be accomplished by the use of *Calcium Phosphorus Co.*, of which three grains, crushed, with at least a full glass of water an hour before food, twice a day, is a suitable dose for an adult. Finally (4), unload the colon, keep the alimentary canal as clean as possible, control the emotions, watch out for the diet, and urge a well ordered and quiet existence—in bed for several weeks or longer if necessary. Until all these procedures have been exhausted, surgery may be a failure, save only in cases of definite thyroid adenoma with thyrotoxicosis, which do not constitute a large percentage of the cases of hyperthyroidism.

I cannot too fully emphasize the importance of *doing everything at once*—the organotherapy without the remineralization, the removal of toxemia, etc., is not going to be especially effective, and I may say the reverse is equally true and many times medical and hygienic treatment which has not been causing very good effects has been made more definitely and rapidly successful by adding the organotherapeutic sedation of the sympathetic irritability as suggested here.

Before concluding this chapter it may be possibly of interest to select a few reports of cases of hyperthyroidism from our records as illustrative of the fact that the treatment recommended by us is indeed able to "make good" in many instances.

A young married woman had a long siege of difficulties with hyperthyroidism which culminated in surgery. About nine months later she came with her trouble "just about as bad as it ever was." We found a bad appendix, which was removed. We neutralized a very decided acidosis (with the *Calcium-Phosphorus Co.* already mentioned) and gave her the sympathetic sedative treatment — *Pancreas Co.*, 1, q. i. d. The results were splendid. The pulse practically never went above 80, and the patient obviously had improved so much that she considered herself well. But—she had a near accident in an automobile; nothing really happened, but for a fraction of a second it certainly looked as though she were going to be wrecked, and within a day or two all her troubles were back again—to my mind, typical proof of the emotional aspects of this difficulty. The same treatment repeated again rendered the same benefit.

A physician in St. Louis reported to me, some time back, a case of a lady with hyperthyroidism whose husband had been told by a prominent surgeon there that the heart muscle had become so weakened that it would be very dangerous to operate on her, but who, following the administration of this routine treatment, "experienced such a change in the heart action, and general betterment that all thought of operation was given up."

About a year ago a California doctor wrote me: "I am now using your *Pancreas Co.* in a case of Graves's disease, and although the treatment has only lasted 10 days so far, there is marked improvement. Pulse dropped from 120 to 87, and there is already much less nervousness and insomnia." A later report indicated that a part of the benefit, at least, has proved lasting.

Here is an unsolicited report indicating the possibilities in certain cases of hyperthyroidism:

"You may recall the prescriptions you advised me to give to a patient who had exophthalmic goitre. For months the patient had been under care of a very good physician and surgeon before coming to me, and the reason for changing physicians was that the patient was told 'nothing but an operation of the thyroid would help.' For some five months I had this patient on your advised prescription [*Pancreas Co.* (*Harrower*) and *Calcium Phosphorus Co.* as outlined in the reprint, "My Routine in Hyperthyroidism"]. Result: Patient gained more than twenty pounds in weight, sleeps well, thyroid hypertrophy now unnoticeable, nervousness disappeared, eyes receded into orbits normally, and patient insists that 'she is well.' "

I hesitate to repeat some of the actual reports for I am already accused of stretching the truth. But I can't resist quoting a case report just received from Nebraska, as I edit this:

"The improvement in the goitre case I wrote you about is so wonderful I could hardly believe my eyes. I put the patient to bed, darkened the room and prohibited any form of excitement. No application was used to the thyroid. *Pancreas Co.* (*Harrower*) was all the medicine she took. Exophthalmos all disappeared, goitre reduced four fifths in size, pulse down from about 200 to 60. No one could become a 'therapeutic nihilist' if he could see this woman's condition—*what she was and what she is now.*"

The foregoing constitute but a sprinkling of many similar typical cases where "definite results" were forthcom-

ing; but I will refrain from burdening the reader by unnecessarily prolonging the list. Suffice it to say that a visit to my office in Glendale would more than repay the time and effort which would be entailed, for we have literally scores of entirely unsolicited testimonials from physicians who have waxed enthusiastic—and rightly so—over the results secured in their patients, not only in the particular disorder under review, but also in the many other dyscrinisms dealt with in this necessarily restricted treatise.

SECTION V. CHAPTER 11

GLANDULAR THERAPY FOR DEFECTIVE CHILDREN

The problems of abnormal growth and development, especially in "children requiring special attention," constitute a very serious and difficult problem in medicine. A famous authority once said, "Throughout the animal kingdom, from the simplest micro-organisms to the most complexly organized beings, that inexhaustible power of growth has remained as one of the most remarkable phenomena of nature, the supreme riddle of life." Ever so often we find a child that is "different," "backward," "abnormal," whose disabilities range from a simple tardiness in certain of the functions of the body to a developmental dystrophy which has caused a material reduction in the size of the body, in its normal development, or in the power to direct it normally. Naturally the classification, "defective children," includes a very wide range of disturbances, and their consideration in a short chapter necessarily must be fragmentary.

The Endocrine Control of Growth. The burden of my remarks will concern the relation of the endocrine glands to these developmental disturbances, and I am convinced that they play a very important part, both in the normal outfolding of mental and physical growth and the physiological changes associated with the metamorphosis from infant to adult, as well as in the pathological modification of these changes. In other words, since the glands of internal secretion are so definitely concerned in the normal growth of the individual, we must expect to have abnormalities in these glands in the defective ones, and if the basic principles of organotherapy will hold good, we should be able to modify some of these defects by applying it.

In the class of cases under discussion, many of the "stigmata" are obviously manifestations of an organic nature and should not be expected to be remedied; but since the underlying element is a disturbed function of some of the endocrine glands, their remarkable responsiveness to hormone stimuli may enable us to bring about some noteworthy organic changes, so that even in these cases organotherapy may assert a definite influence upon structural as well as functional defects.

In children, particularly where there is a developmental defect and various evidences of malnutrition connected with a disturbed function of the endocrine glands, and where dermatoses are imposed upon these individuals, the regulation of the endocrine aspect sometimes disposes of the dermatologic trouble simultaneously and oftentimes miraculously. A study of the endocrine aspects of any individual often adds much to our knowledge regarding him, and broadens the prospect of his treatment.

The miraculous changes in the athyroid cretin made possible by the use of thyroid extract, have been one of the most magnificent advances in medicine, and it is well known that children who have the typical manifestations of hypothyroidism can be made to grow and develop in a wonderful manner by supplying the missing hormones. It happens, however, that hypothyroidism, pure and simple, is rare, since the absence of the usual thyroid stimuli cannot but have a serious influence upon other endocrine glands ordinarily dependent upon these stimuli; hence *the cretin is never solely a thyroid case.* The same applies to disturbances of other glands, notably of the pituitary. It has been shown that the pituitary gland exerts a remarkable influence upon growth and sexual development, and the principal manifestations of deficient pituitary function are a tendency to adiposity and sexual mal-development—the adiposogenital dystrophy of Froehlich. The diagnostic side of this subject is more thoroughly considered in Section IV, Chapter 6.

Which Cases Respond to Organotherapy? The differentiation between those defective children that are likely to respond to organotherapy and those in whom there is no likelihood of benefit is very difficult, and it is a very serious thing to doom a child to lifelong disability by saying that this method of prospective merit, or that, need not be employed because it is useless. As a matter of fact, case after case has come to my attention whose parents have

said, "My Doctor says there is no hope for Willie, because he has given him thyroid for years, and while he benefited for a while, he isn't any better in the last year or so and I am quite discouraged." In cases like this, the usual trouble is a "sin of omission." The interrelated glands have been ignored, and dependence has been placed upon thyroid alone when, in fact, the thyroid element in the case was but a part of the syndrome. Again, errors in diagnosis are possible, even by the greatest of authorities and there has been quite considerable confusion regarding the treatment of these cases, largely because of the limited viewpoint of many observers. Now that a large amount of work has been done with the pituitary gland, the aggregate of results is beginning to be considerably better.

A source of trouble concerns the determination of cerebral difficulties. If there are definite changes in the character of the cerebral cortex, or if there are developmental defects in the cranium, which naturally prevent cerebral growth and function, the prospects are not good, and many idiotic children are quite hopeless for this particular reason. The hypocrinic child, on the other hand, is merely sluggish, not idiotic or demented, and his physiology is merely retarded, and it has been shown that even the growth is not permanently arrested, which is proved by the fact that thyroid, or other organotherapy, completely changes the clinical features. There is always a possibility, however, that a child definitely defective from a cerebral standpoint may have associated with this trouble a sufficiently important endocrine phase to make it worth while to attempt to modify it, and I have come to the conclusion that it is more proper to attempt organotherapy in those cases in which the prospects are poor, than to deny the parents this "last straw."

I am sometimes asked if our preparations would be helpful, say, in the case of a boy of 15, who, while not deformed, may have only attained the height of an average child of ten. In cases of this kind, if there is a possibility that the boy has attained his maximum growth and therefore may not respond to organotherapy, it is possible to make an X-ray picture of the hand and note from it if the epiphyses are joined or not. If they are joined completely, the chances for growth are not so good; if they are not joined, there are very good possibilities of increasing the height. Some of the cases elsewhere reported in this chapter will prove interesting reading in this connection.

Some Results From Glandular Feeding. Since pluriglandular disturbances so generally are the rule and it has been shown that the thyroid and pituitary glands are related in the causation of developmental dystrophies, it seems highly advisable to combine preparations of these glands rather than to administer them singly. I have shown in my "hypothesis of hormone hunger" (Section II, Chapter 4) that a mixture of extracts when given to the body is made use of *in proportion to the demands,* and that it is presumable that moderately superfluous quantities of these substances remain in the circulation until the time comes for their use, or they are oxidized. At all events, the pluriglandular feeding of defective children has been a good deal more successful in my hands, as well as in those of a good many of my friends, than thyroid or pituitary or thymus alone, all of which have been recommended in the literature as of use in these cases. I have therefore combined these preparations in suitable amounts in a combination now known as *Antero-Pituitary Co.* (*Harrower*), each dose of which contains 2 grains of the desiccated anterior lobe of the pituitary body, 1 grain of thymus, 1-12 grain of thyroid, with the mineral salts which correspond to those found in the blood. This formula has been used in many defective children, and if there is no cerebral difficulty, as in idiocy, the backwardness of mentality and the development may be modified by it, for defective children always have a well-defined endocrine feature. I have seen a number of cases in whom it was eminently successful—of a child of two or three years, previously unable even to sit up, who has not only learned to sit and crawl, but to walk; of children of five to seven who had never been able to speak, who in six or eight months were able to make intelligible sentences of five or six words; of children of eight years who had been persistently constipated from birth and who "had never had a normal bowel movement in their lives," whose alimentary conditions were modified and the constipation entirely controlled without cathartics. (Parenthetically, it may be well to state that one of the common manifestations of endocrine deficiency is cellular infiltration, muscular atonicity and asthenia, all of which very definitely favor chronic alimentary insufficiency and stasis.)

An Interesting Case. I cannot refrain from alluding here to a case which I believe has already been quoted in some of my literature: that of a four-year-old defective child who was brought to me by a lady for study and suggestions.

In doing this she was acting on the recommendation of a physician who had been converted to the reasonableness of my ideas. The boy could neither speak, walk, nor even sit up; he had no control over the bowels or urination, had very poor powers of perception and was regarded as an idiot, with no chance whatever. He was treated for several months, on and off, with *Antero-Pituitary Co.* (*Harrower*), the parents being told that this was a gamble and was suggested on the off-chance that the boy might have a sufficiently definite endocrine phase to the difficulty to make it possible there might be some worth-while benefit. Emphasis was laid on the large chance of failure. The parents, being desperate and without hope, elected to "try me out." When I next saw the boy he was able to walk, run, sit up, and climb like a normal boy, and his mentality had developed amazingly. While he could not speak plainly, and probably will never be able to do so, the bother of having to transport him from place to place was a thing of the past. He has better intelligence and is a source of greater joy to his parents, and, though much is still to be desired, they felt very grateful for what had been done. This story had a strange aftermath. The mother's aunt was a physician's wife. The worthy physician passed judgment on the case, and it was unfavorable! He also passed judgment on me and the phase of medicine that we are trying hard to develop. This, too, was unfavorable! In fact, he urged them against consulting me and, a few months later, advised them to abandon my treatment. And now the doctor, according to the mother, says: "Well, it might have happened anyway"! Such is life.

I may perhaps be pardoned for quoting another case brought to our notice by a Maryland physician: A defective girl of nine, who had never spoken, and who had to be supported under the arms in order to take a few steps, which she could not do volitionally. When our medical correspondent first took her in charge, the tongue seemed to fill the whole mouth and rested on the tip; there was constant drooling and she could swallow with difficulty. It was quite impossible to see the tonsils. Her elbows and wrists were semi-flexed, and while she could stand by being propped up in a corner, she always rested on the tips of her toes. Apparently impressions were received through the ears. Constipation was marked and the urine scanty. Her parents had had the best specialists in Baltimore, and the prognosis was that she "might walk but would never

talk." The doctor went on to state that two months after prescribing *Antero-Pituitary Co.* (*Harrower*), the child's tongue had come down to normal size, and the soft palate had been taken up to its proper height. The whole expression of her face was improved. The head, unfortunately, was about two inches too small, but he was hoping there might be an energizing of the whole skull. Certainly, he added, the seeming exostosis above the eyes had vastly improved in appearance, and, "while there is life, there is hope." She had better accommodation of vision and could already see about 12 inches from the eyes. The guttural sounds emitted had taken on a higher pitch, and she could stand on both feet with fairly good arches—assuredly a great improvement. In commenting on this in one of my other publications I opined that this child had a large thyropituitary aspect to the underlying disorder. Certainly no other measure, save organotherapy, could have brought about marvelous changes like those mentioned. With the good doctor, "I have no promises" to give these people, but surely the prospects for still further improvement are far brighter today than, say, three months ago.

Remarkable Growth Stimulation. I have seen children who have attained the age of fifteen or sixteen, with no growth whatever for five or more years, suddenly begin to grow and change following the application of this formula; in one case as much as one inch in 9 weeks—another, that of a defective girl of five who could not speak and who after using the formula, in 6 months was making five and six-word sentences, with other improvement. I recall one boy in particular who was fifteen and a half when I first saw him; height four feet four inches; general contour stubby and ugly, with a temperament that was very unfortunate—he was almost impossible to get along with. His liver was stimulated a little (with my *Bile Salts Co.*, referred to elsewhere) and the *Antero-Pituitary Co.* (*Harrower*), was given, with the result that within four months he had gained two inches and, better still, his temperamental difficulties disappeared. A letter from Washington, dated Jan. 13, 1920, contained the following item of information: "Our backward boy has gained three inches in height and is doing much better in school. He began taking the *Antero-Pituitary Co.* last June."

Another striking case was that of a girl of nearly 15, development and height those of a girl of ten, who grew four inches after taking this formula for less than three

months. I have seen infantilism in children at puberty modified by this formula or another similar to it containing extracts of the gonads. In fact, in these grown-up children that do not mature, not merely is a satisfactory development possible, but in some of the older ones fecundity actually has been established. Finally, a number of these peculiar children in whom the general symptom-complex included epilepsy, both of the *petit mal* and *grand mal* types, not merely have changed from a morphogenic standpoint, but the epileptic seizures have been entirely controlled. This subject is taken up more fully in the chapter entitled "Epilepsy from an Endocrine Standpoint," which follows.

Persistence is Necessary. To determine in advance how well this treatment may work is impossible, for medical men are not prophets and have no way of knowing exactly what endocrine disturbance is present nor how well these glands may respond to suitable stimulation. Hence, it is necessary to explain to the parents that while results have been favorable, one cannot predict accurately. It is the rule for these parents to ask how long it will take, and one cannot answer definitely. They practically always ask to what degree this symptom, or that, may be controlled, and it is equally impossible to say. It is my custom to tell them that since this measure has been effective before and as they have never tried it yet (for most of them come after having used a single gland extract or followed organotherapy for a few weeks or months), it is worth trying and we will hope that the results will be good. They should be told by the physician that this is "the most hopeful side of attack"; that endocrine insufficiency has been connected with conditions similar to the one in mind; that the formula to which attention is here drawn has made many physicians pleased and brought joy to many a mother, and that it is to be hoped that in this particular case the outcome will be good also.

At all events, in all these cases the real attempt is to reëstablish the deficient functions — to educate certain glands; and this form of education, as with all other forms, takes time. Gland feeding must be continued for a minimum of six months. It is useless to commence unless you can secure a promise to stick to it for this length of time. It must be given regularly and the results must be watched carefully and, if necessary, the treatment modified to suit the changing conditions. Naturally, every associated effort to favor the desired outcome should be advised, and particu-

lar attention should be paid to elimination and to the metabolism of the mineral salts, a subject which has been considered in another chapter—"The Mineral Salts in Health and Disease: Remineralization." (Section V, Chapter 25.) To accomplish this the use of *Calcium Phosphorus Co.* (*Harrower*), is recommended.

The dosage is usually three 5-grain doses, at meals; the former in children under six months will suffice for a time. I am in the habit of prescribing this formula to be taken for four out of every five weeks. During this period of treatment, if the symptoms of thyroid insufficiency predominate, I would add from one fourth to one half grain of thyroid t. i. d.

In conclusion, I want to emphasize my position about recommending this treatment. It is a chance; it fails probably more often than it succeeds and the "successes" might not always be quite satisfactory to a critic. I know that its application has caused joy many times; and such joys far outweigh the failures—and cannot be attained unless we try.

SECTION V. CHAPTER 12

EPILEPSY FROM AN ENDOCRINE STANDPOINT

It seems to be the custom, since the endocrine glands and preparations have done so many wonderful things, to expect to find help from them in all puzzles that we have failed to solve for years. This may be all very well, and occasionally we stumble over some remarkable things which keep up our courage, but when it comes to expecting a consideration of the ductless glands and organotherapy to give us the *open sesame* to the mysteries of insanity, paralysis agitans, dwarfism, sterility and epilepsy—all of them "hard nuts to crack"—it almost seems that we are asking too much. Yet the fact is that there are greater prospects today in the treatment of every one of these mentioned conditions from the endocrine standpoint than from any other procedure considered up till the present time.

Epilepsy: "The Mysterious Disease." Epilepsy is one of the big puzzles of medicine. We have a lot to learn about it, even though our more recent knowledge about the dietetic and toxic (alimentary) causes is growing, and the relation between the glands of internal secretion and the epi-

leptic syndrome seems to be receiving much more attention. The universal dependence upon the bromides or other neurosedative drugs is a poor makeshift, and altogether on a par with the morphin injection for an access of pain. Such an injection does not cure the disease, any more than bromides cure epilepsy. But when someone comes along and says that certain gland feeding has been accompanied in one case of undoubted epilepsy by a reduction of the number of attacks, 50 per cent., 75 per cent., or even more, we have a perfect right to "sit up and take notice."

It will be my effort to emphasize the importance of the disorders of the ductless glands as they may pertain to epilepsy and to suggest—not to announce—a treatment which may give us a greater degree of satisfaction in epilepsy than the unscientific and truly disgraceful method of stuffing the sufferers with bromides morning, noon and night.

Is there any relation between disturbances in the glands of internal secretion and epilepsy? If so, there may be some hope, and a statement of some of the findings in the literature may give us reason for applying this principle in our treatment of epilepsy.

A Thyroid Factor in Epilepsy. It has been shown in many communications that disorders of the thyroid gland may be accompanied by epilepsy. In a paper entitled "The Relation of the Thyroid Gland to Epilepsy" (*Lancet-Clinic*, July 29, 1916), I collated a good deal of information which seemed to establish the belief that hypothyroidism was a factor in the cause of epilepsy and that when an epileptic was found with an associated hypothyroidism, the treatment with obvious organotherapy—thyroid extract—might have some beneficial influence upon the epilepsy also. Gauthier, in his book, published in 1913, has gathered many communications in French medical literature, and a brief quotation from this should suffice: "Epilepsy is considered by a large number of physicians and neurologists to be an intoxication, or a general disorder of the metabolism. There is also a possible connection in certain cases with the work of the thyro-parathyroid combination. The association of epilepsy with myxedematous idiocy, cretinism and even Basedow's disease is well known. But there are other evidences. Many cases of simple goitre become epileptic and goitrous mothers give birth to epileptic children. Claude and Schmiergeld, in a study of seventeen cases of epilepsy from the endocrine point of view, have found in

every case alterations in the thyroid gland and in twelve of these the structure of the gland was completely altered with the areas of sclerosis and limited zones of compensatory hypertrophy of the glandular tissue. . . . Parhon examined the thyroid in twelve epileptics, and found it smaller than usual and showing frequent and variable histologic changes." Many other convincing experiences and references will be found in the third issue of *Harrower's Monographs on the Internal Secretions*, which is entitled "Epilepsy as an Endocrine Syndrome." (This 80-page publication will be sent on approval to any interested physician.)

From the information gathered together here and elsewhere, we are justified in drawing some conclusions:

1. That the thyroid insufficiency is likely to be a frequent underlying factor in the etiology of epilepsy for several reasons: (a) It favors toxemia; (b) it produces cellular infiltration and edema, which may affect the brain in the manner described by Hertoghe, Reed and others, and (c) it usually causes other sypmtoms in epilepsy which have been definitely attributed to hypothyroidism.

2. Thyroid therapy is a rational therapeutic adjunct in the treatment of epilepsy accompanied by other signs of hypothyroidism.

3. Favorable results from the use of thyroid extract in epilepsy should be considered as a confirmation of these conclusions.

Involvement of the Pituitary Gland. Still another gland of internal secretion has something quite definite to do with epilepsy. This is the pituitary gland, a mysterious organ which regulates many functions of the body and about which practically all our knowledge has been developed in the last fifteen or twenty years. Just why the pituitary should cause epilepsy does not seem to be very clear save only as increased intra-cranial pressure from an enlarged gland might cause pressure upon local structures which, in turn, might cause the typical experiences which we call epilepsy. Some writers have thought that the circulatory disorders quite common in epilepsy—slow pulse, vasomotor stasis, low blood pressure, with a tendency towards obesity and an abnormal appetite—are somewhat similar to conditions which obtain when there is well defined pituitary disease. Harvey Cushing, the world's best authority on the pituitary gland, gives six reasons why pituitary insufficiency is related to epilepsy. In brief, they are as follows: (1) Horsley, of

London, noted increased excitability of the motor cortex in hypophysectomized dogs. (2) Epileptiform convulsions were frequently seen in animals which survived for long periods after partial removal of the pituitary (Cushing). (3) "Epilepsy is a frequent accompaniment of clinical conditions in which an insufficiency of the pituitary is manifest." (4) The pituitary may be damaged from a bursting fracture of the base of the skull. (5) It is believed the posterior lobe secretion enters the spinal fluid, thereby bathing the cortex with a substance essential to the functional stability of the cortical cells. (6) "Many individuals, supposed to be suffering from so-called genuine epilepsy, present symptoms of pituitary insufficiency and in some of these, pituitary extract has served to moderate the seizures." Based upon these conclusions, a good deal of experimental gland feeding has been done in epileptics, and certainly far better results have been obtained than before this matter was given consideration.

Adrenal Irritability. Still further study of epilepsy has involved other glands, and Cotton, at the New Jersey State Hospital, has come to the conclusion that there may be an unusual irritability of the sympathetic system due to the action upon the adrenal glands of poisonous products from the intestines. Further, according to Cotton, adrenal activity also may be caused by (1) pituitary dysfunction, (2) pancreas dysfunction, (3) irritation of the duodenum, and (4) severe fright or emotional disturbances. His idea was to antagonize the adrenal irritation by the use of the normal antagonist to these glands—the pancreas—and preparations of this character have had "a decided effect in stopping the convulsions."

Possibly other glands have been connected with epilepsy, but in order not to complicate an already complex matter we will continue our study of the propositions discussed.

Evidently there are several underlying or exciting causes of epilepsy that are connected with the glands of internal secretion, and whenever it is possible to discover some endocrine disturbance in an epileptic, the rational thing to do is to attempt to modify it as quickly as possible. Unfortunately, however, we cannot always assure ourselves of the presence of these disturbances and the patients have well-defined epilepsy and want help, and I am sorry to say that most of use heretofore have been giving nerve paralyzants or sedatives as recommended in the text books. "What else is there that we can do, anyway?"

I believe that it is no more unscientific to presume that a given endocrine disturbance may be the underlying cause of epilepsy and to treat it experimentally, than it is to fill the patient up with a drug that we know perfectly well does not go to the bottom of matters and, worse still, is insidiously destroying functions (especially mental) which may not be restored, once definitely damaged.

The Endocrine Element in Epilepsy. I do not think that it is wrong to "jump a ditch" once in a while or, in other words, to attempt to accomplish some end in a manner that we cannot accurately explain or predict the outcome of. This means that *I believe that endocrine disturbances are sufficiently commonly associated with epilepsy to warrant our using means ordinarily applied in the treatment of these endocrine disturbances as a part of the treatment of such cases.* If the motor excitability is tremendous, we must use sedatives just as we use an anesthetic in eclampsia, but always as a part of a treatment which has a greater prospect of the results than the sedative itself alone.

How are we to know what glands to give in epilepsy? Several phases of the subject are mentioned and they seem to differ quite considerably. It is not difficult to establish the fact that a given individual is suffering from thyroid insufficiency. If it may not have reached the stage of the usual symptomatology, there can be no objection to using Harrower's "Thyroid Function Test" (Sec. IV, Chap. 4) and seeing how the individual reacts to this. We have no way of connecting the pituitary gland with a given case of epilepsy save by the usual study and examination (Sec. IV, Chap. 6) and, perhaps, the administration of the gland on a chance. The condition of adrenal irritation discussed above properly may be treated by the removal of all causes of this condition, especially toxemia, by antagonizing the adrenals, if it seems advisable, in harmony with Cotton's suggestion, and particularly by increasing oxidation by enhancing thyroid and pituitary function so that the accumulation of poison will not drive the adrenals so hard.

Treatment of Ovarian Epilepsy. For 20 years it has been suggested that certain forms of epilepsy are definitely connected with dysovarism. Clinical experiences have shown also that the thyroid as well as the pituitary may be involved in this difficult condition. If there is a decided endocrine aspect to any patient with epilepsy it is surely correct and proper to attempt to modify the endocrine condition, and then if the epilepsy is simultaneously benefited every-

body is satisfied. Therefore, in cases where there is an ovarian element, instead of treating the epilepsy, try to regulate the ovarian condition. I have several interesting cases on my records, one of which may be mentioned here: A physician had a case of epilepsy which was not responding to treatment. After a long time, it seemed that there might be some relation between the convulsions and the ovarian function and my *Thyro-Ovarian Co.* was given. The physician writes me as follows: "My patient, Mrs. C., age 45, had for the past five years been suffering with headache and epilepsy. These fainting spells made their first appearance after a miscarriage and have kept increasing in number until it was not unusual for her to have six, eight or even more a day. Various remedies were tried without much effect until I put her on your *Thyro-Ovarian Co.* and the results have been most surprising. The patient tells me she has not had one attack since starting this treatment, which naturally pleases me very greatly." Evidently this patient had a well-defined dysovarism which, when treated, so modified the chemistry and nervous susceptibility that the attacks were controlled.

Success in Certain Cases of Epilepsy. As some of my friends know, I have been interested for years in what might be termed "experimental organotherapy", and the most important part of my work has been the development of various pluriglandular remedies for the treatment of certain conditions which I felt sure were of endocrine origin *and involved several of the ductless glands* rather than the most obviously disordered alone.

One of these formulas was intended to awaken the dormant growth and development capacity in defective or backward children. Without going into details—which have been outlined quite fully elsewhere, as, for example, in a foregoing chapter (7)—I may say that this preparation of anterior pituitary, thymus and thyroid has served unusually well in modifying those aspects of these unfortunate children which are due to ductless glandular dystrophies.

Not infrequently epilepsy is one of the findings in these cases, and, while it may be purely "idiopathic", it is found sufficiently often to be considered as more than coincidental. As a matter of fact, the dyscrinism, i. e., disturbed function of the endocrine organs as a whole, may be just as much a cause of the epilepsy as of the stigmata and developmental difficulties. The thyroid and the pituitary repeatedly have been charged with bringing about conditions which

favor epilepsy, if, indeed, their dysfunction may not be the actual cause.

At all events, this formula for defective children—*—Antero-Pituitary Co.* (*Harrower*)—was used in a number of this type of cases in whom epilepsy was also present, and we were both surprised and delighted to note changes in the severity and frequency of the epileptic attacks.

After a few months it was considered worth while to use this same treatment in epilepsy not obviously associated with a nameable endocrine difficulty; in other words, we said to ourselves: "Here are cases of epilepsy with noticeable difficulties known to be the result of endocrine disorder, and treatment directed at this phase is helping the epilepsy as well. Why might not there be a less obvious but just as real connection between these glands and the epileptic syndrome in cases where the developmental or other stigmata are not seen?" It was empirical, I admit. We based our work on reasoning, rather than known physiology (for we had no way of determining which glands were at fault and to what degree), and are still being criticized in some quarters for unscientific "shotgun" therapy.

But, literally scores of cases of epilepsy—not merely in children, as we had planned to limit this therapeutic testing, but in youths and adults of both sexes—have been benefited in a remarkable degree. The attacks have ceased altogether in many instances. In others, their character has been entirely changed and the treatment is being continued. In still others, especially in cases where it seems quite sure there is a definite structural cerebral lesion, there has been no benefit worth mentioning.

I have scores of case reports that I could mention—names can be given if it is desired. I have had some experience myself, and confess that in some of the cases where I felt compelled to give this formula, I did so with misgivings, and frankly told the parents that it was improbable that there would be any results. In every instance they had come expecting that whatever I might recommend would be tried out as a last hope; *and in every case, so far, I have secured benefit,* even if all were not "cured"—though some undoubtedly have had the attacks stayed now for many months where, before, they came on several times each day or week.

I have already called attention to the fundamental reasons for this, and have quoted from authorities like Cushing, Léopold Lévi, Hertoghe, Gauthier, and others. It is undoubted that there *may be* a thyroid cause for the toxemia so com-

monly associated with epilepsy; that there *may be* a definite pituitary cause also, and there *may be* other disorders of this type needing attention in those who also have epilepsy.

How are we to determine which cases are suited for this treatment? Frankly, I do know how to do it—*in advance!* But is it any the less improper to apply pluriglandular therapy with a fairly encouraging prospect of results than to give bromides?

Some Clinical Reports. I know just how some physicians feel about clinical reports—they discount them, refer to the need for "controls" and many won't listen to them at all. Anyhow I am going to pass along a few unsolicited reports of cases treated with *Antero-Pituitary Co.* (*Harrower*). Believe them, or not, as you wish.

The first was published in the *New Orleans Medical and Surgical Journal,* and an abbreviated outline follows: The case was so-called "idiopathic epilepsy" and was reported by Dr. J. E. Isaacson at a meeting of the staff of the Hotel Dieu, New Orleans, held July 11th, 1921. The subject was a lad of sixteen who at one and a half years of age, while suckling, appeared to be taken with a convulsion. Similar convulsions occurred on and off until he reached the age of five years, sometimes as many as four or five spells a day being experienced. After observation and treatment by various pediatrists and psychiatrists he was, as a last resort, sent to a mental institution and placed in a straight jacket. After one year's confinement there, he returned home for two months, subsequently returning to the institution whence, after four months, he was discharged as incurable.

The case was a most unusual one, in that for four months preceding the time the patient was taken in hand by Dr. Isaacson he had lost all control of bowel and bladder functions and appeared to be in considerable pain judging from the writhing movements and cries observed.

The physical examination revealed "an under-developed and poorly nourished, white male with facial characteristics of an old man." Urinalysis, feces and blood test (Wasserman) negative.

The way the patient responded to the treatment immediately instituted (viz: antero-pituitary body compound) was really wonderful. The therapy was based on the fact that "idiopathic epilepsy" is often due to pituitary deficiency. Starting with an initial dose of five grains of *Antero-Pituitary Co.* (*Harrower*) three times a day, Dr. Isaacson states (*New Orleans Med. & Surg. J.*, Sept. 1921, p. 210):

"Strange and amazing as it may appear, from the time of the administration of the first twelve doses, there has been an absolutely steady improvement, which heretofore has been unobtained from any and all medication. At present date (July 12th), the fourth month after initial dosage, said patient is up and about, having complete control of all body functions, and having gained 34 pounds in weight. The vomiting has entirely disappeared, the patient eats everything, including ant. pituitary. Is able to do the ordinary chores about the house, run errands, and can now write and spell the primary lessons."

He concludes by urging a fairer consideration of treatment of this type by his critical colleagues and stated that there has been no recurrence of the fits, where previously four or five a day occurred.

An Encouraging Letter. Quoting from another letter: "To show you that I believed in what you were doing is but to mention that in the last five months I have been using your preparations and I have practically cured nearly 20 cases (of epilepsy) and in general have been meeting with almost unbelievable success. One case in particular will interest you: I saw this boy while he was suffering the rigors of influenza, and after treating him for this for a few days, his mother asked if I would not try to help his epilepsy. At this time the child was having 15 to 30 convulsions a day, both the *grand* and *petit mal.* The situation did not look good to me, as he had been seen by nine nerve men who had given the mother no hope whatever. He had been circumcised and had had the tonsils and adenoids removed a year prior and had been on a diet and bromided so that he had almost no life in him.

"I modified the diet, cleaned him out some more and gave one of your combinations, and from the first week of this treatment to date, he has had no return of the symptoms, the only trouble being that from a pallid invalid he has changed into the worst youngster in the neighborhood! This I consider my most remarkable case, for it seemed like a miracle to cure this child."

Several more from quite a large number accumulated during the years may be added:

"I have been using your products about one year and have obtained most flattering results. In one case I have succeeded in keeping off epileptic attacks of the most desperate character for a little over a year, having given comparatively small amounts of *Antero-Pituitary Co.* (*Har-*

rower) during this time."

"One case of epilepsy I have had under treatment for eleven years and the *Antero-Pituitary Co.* (*Harrower*) is the first treatment that has given me favorable results. Another important case that I have had under my care for six years is doing splendidly, and for the first time in all these years has had no attack for three months."

"The surprising result I have had with your capsules in the case of my niece has made me intensely interested in the study of epilepsy and I now desire to carry on some scientific work with it. My small experience with your formula in other cases besides my niece has led me to agree with you that back of epilepsy is a disturbance in the balance of internal secretions."

"Amazing and strange as it may seem, from the first five doses—which were given as charts in the beginning—a steady improvement has been noted and now in less than two months said patient is up and about (out of bed for first time in four months) has complete control of all body functions, gain of 21 pounds, no vomiting, and eating everything including *Antero-Pituitary Co.* (*Harrower*). Lastly, absolutely no 'fits' in past three weeks whereas he formerly had five to six attacks a day; mind is clear and patient rejuvenated."

Not a Panacea. I do not wish it to be understood that I am recommending this formula, or any glandular extract, as a "cure" for epilepsy or anything else. I merely state that it has been used with distinct benefit in a number of cases; that there is enough in the literature, a small part of which I have collated (both here and in the second issue of *Harrower's Monographs,* already referred to), to give some sort of a reason for this method of treatment, and, finally, since the prospects are so poor anyway, and there is a chance from this treatment, why not give it, since two or three doses a day are not known to have caused any detrimental effects and certainly cannot be compared to the use of the bromides? Unfortunately, not every case is going to respond to this treatment, but one single success will outweigh a hundred failures.

The usual dose for small children is two five-grain doses a day, while to children above five years, two or three a day is proper. Individuals with well-defined thyroid insufficiency may need additional thyroid extract. It is useless to start this treatment unless it is accompanied by proper dietetic, hygienic, and especially eliminative, treatment. It must be

continued for months, and I am in the habit of prescribing this formula for four out of every five weeks.

Conclusions. To put it succinctly: Epilepsy has been entirely cured by the administration of *Antero-Pituitary Co.* (*Harrower*). It is going to be again—often, I hope.

I urge the following points:

(1) A reasonable attitude.—Organotherapy does not sedate over-irritable cells, and, hence, cannot take the place of bromides for this particular purpose; also, it is only likely to be of value in those cases where there is indeed an endocrine element present;

(2) Persistence.—Treatment should not be started unless the parents agree to follow it for at least six months;

(3) Detoxication.—By every known method—dietetic hygienic and medicinal.

SECTION V. CHAPTER 13

NOCTURNAL ENURESIS

There are, perhaps, a dozen references in the literature indicating that clinical experience has convinced various writers that nocturnal enuresis has an endocrine aspect.

Leonard Williams' Ideas. In his interesting book, "Minor Maladies," Leonard Williams, of London, calls attention to the above point in the following words: "As the child progresses in years, deficiency in thyroid secretion may reveal itself in various ways. One of the most dramatic and alarming is the production of night terrors. I do not pretend to be able to explain the association between these unpleasant ebullitions and a deficiency of thyroid essence in the circulation, but I can most positively affirm that they rapidly disappear under the influence of thyroid extract. I have already shown that nocturnal enuresis ('Adenoids, Nocturnal Enuresis and the Thyroid Gland,' London 1909, Bale, Sons and Danielsson, Ltd.), though it may own other causes, such as phimosis or intestinal worms, is in the vast majority of cases caused by thyroid inadequacy and is readily curable by the administration of thyroid extract."

This same writer has published several other articles lending emphasis to his opinion that there is a decided thyroid side to many cases of nocturnal enuresis, and if the

physician will consider carefully the thyroid aspects of his case, often other proofs will be forthcoming and the treatment will not be directed alone at the bed-wetting, but at the complete syndrome of which it is believed the enuresis is but a part. It may be well to go into a little more detail in regard to the thyroid basis of nocturnal enuresis. It is well known that many children with definite stigmata of hypothyroidism, do not have good control over their urination, and especially during sleep. It is also known that many of the children who are backward or in the large class called "children requiring special attention," have as one of their symptoms this nocturnal enuresis. When a child is run-down and especially depleted from a sympathetic nervous standpoint, this symptom is likely to be seen.

Hertoghe's Bladder Desquamation Theory. In addition to Leonard Williams, who has already been quoted, Eugène Hertoghe, of Antwerp, and Léopold Lévi, of Paris, both have written convincing articles assuming a definite thyroid cause for bed-wetting. Hertoghe has explained this, perhaps, as intelligently as any. He says that in fairly well-defined forms of hypothyroidism there is a marked tendency to cellular infiltration. This does not limit itself to the skin, as in myxedema, but involves among other parts of the body the mucosal covering of the bladder. These squamous cells become infiltrated and, therefore, die more readily and are desquamated into the bladder, causing an increased amount of cellular debris in the urine (which may be found by microscopic examination) and a more decided irritability of the recently denuded bladder walls to the urine that may be present. This naturally causes an irritability of the bladder and favors the nocturnal enuresis.

Other explanations have been given for the relation between the thyroid gland and bed-wetting in children, and it may not always be possible in advance to determine that a given child has a definite thyroid cause for the trouble which may bring it to your attention. In harmony with Léopold Lévi's suggestion, it is well to give cases of this kind a course of thyroid therapy in the hope that this may modify the presumably underlying dysthyroidism and at the same time favor control of the enuresis. This is in harmony with my suggestions in the chapter entitled "Diagnostic Organotherapy" (Section II, Chapter 6), in which I urge the application of a suitable glandular feeding in the expectation of acquiring information in regard to the basic cause of the trouble, as well as attempting to benefit it.

Léopold Lévi recommends the beginning of the opotherapy of such cases with approximately a quarter to half of a grain of thyroid a day. I have frequently recommended a quarter of a grain three times a day, and increased this dose sometimes to 1½ or even 2 grains a day.

In children that are definitely abnormal the principal effort should be made to modify the fundamental endocrine imbalance in order that they may be more nearly normal, and this we have been in the habit of doing with *Antero-Pituitary Co.* (*Harrower*), which has been discussed quite fully in previous articles and especially in the chapter entitled "Glandular Therapy for Defective Children."

The Posterior Pituitary Principle. There are a number of references in the literature which indicate that the principle of the posterior pituitary lobe has a tonic influence on the bladder muscular cure and has been used successfully in the control of nocturnal enuresis. Injections of *Liquor Hypophysis, U. S. P.,* frequently have been given with definite control over bed-wetting and for reasons that are not always easy to explain. Perhaps there is a deficient tonicity of the bladder muscles, and especially those muscles concerned in the retention of the urine; and the well-known musculotonic influence of this principle has served to bring about a better turn and, therefore, increased the facility of control of the urine in the bladder.

I recall the case of a student nurse, age 20, who had never overcome the habit of her childhood. It was so mortifying to her that she was in a serious nervous state as a result of the obvious emotional factors. I was consulted by one of the hospital faculty—advised *Liq. Hypophysis* "on the off-chance that it might help her" and six injections cured her entirely.

Provided the external conditions are ruled out of the diagnosis, that is to say, if there is no local condition, no intestinal worm, no phimosis, no central nervous lesion, and provided, generally speaking, that the case has been brought into the prospectively endocrine class, the thyroid feeding should be given for at least a month.

A Suggestive Routine Procedure. There is a little scheme that I have suggested which may be well worth passing along. If it is presumed that there is a thyroid or pituitary basis for conditions of this kind, prescribe one hundred *Thyroid Co.* (*Harrower*) No. 9, representing one half grain of the desiccated thyroid substance. Give one such dose each day for a week, usually with the morning meal. During the

second week, give one at each of two meals, and, during the third week, give one at each of the three meals. During the fourth week of this clinical test, give four doses a day, and during the fifth week omit the thyroid entirely. During this entire period have the patient, or parents, make a record of conditions as they show themselves, and note if during any of these weeks there is any special change in the bed-wetting. Watch for the tolerance to the thyroid, and thus discover the optimal dosage required. At the end of this five-week period, if there is no change at all, another plan may be suggested. Secure a package of *Liquor Hypophysis* (*Harrower*)—a 15-mil. vial—and inject hypodermically five minims, every other day, for a week. During the second week, give eight minims at each dose, daily. At the end of the second week it will be possible to pass judgment upon the efficacy of this measure and, if there has been some benefit, it may be continued. Otherwise, we will conclude from our seven or eight weeks of experimental organotherapy that these two endocrine aspects, at least, evidently are not at the bottom of the difficulty.

Quite often the thyroid therapy alone exerts a very satisfactory influence upon a nocturnal enuresis that has proved resistant to other methods of treatment. Leonard Williams is very decided in his statements about this. On the other hand, a number of cases that do not respond to thyroid therapy have been cleared up with the posterior pituitary principle as suggested. Success in the treatment of conditions of this kind by organotherapy involves the pinning down of the difficulty to an endocrine cause, for organotherapy will not modify a nocturnal enuresis of some anatomical, mechanical or chemical basis; and here, again, is an instance of the diagnostic organotherapy already referred to.

SECTION V. CHAPTER 14

HEMOGLOBIN: A REMEDY FOR ANEMIA

One of the oldest forms of organotherapy was represented by the treatment of various affections by using fresh blood from various animals and birds. As late as twenty or twenty-five years ago, this treatment of anemia, and especially tuberculosis, was quite a common prescription; and,

despite their repugnance, the patients made their daily trips to the abattoirs in order to drink the blood warm from the animal. The development of a technique in organotherapy, and especially vacuum methods of drying, have put an end to all this, and repurified oxyhemoglobin in powder or solution is now available.

Some Physiological Considerations. Hemoglobin, or oxyhemoglobin, is the respiratory element in the red blood cell and is the principal source of iron in the body. The richness of the hemoglobin in the cell, and consequently the richness of the iron in the blood, controls the "respiratory value" of the blood or, in other words, determines its value as a means of taking oxygen from the air to the various tissues and bringing back carbon dioxide for elimination. Modifications in the hemoglobin content in the blood necessarily must be of serious moment, and the condition known as anemia is not merely a disturbance of the number of blood cells but of their hemoglobin content.

For many years, metallic iron (reduced iron) and various salts of iron have been recommended for their "hematinic" value, and among the better known of these is Blaud's mass, containing carbonate of iron; ferric chloride, usually given in the form of the tincture, and a large number of so-called "organic" forms of iron in which iron has been combined with proteids like casein, albumin, etc.

A great deal of experimental work has been done to determine the physiological availability of the iron in various iron preparations, and it has been shown that the majority of practically all of them, both organic and inorganic, is largely passed out in the stools unchanged or, at least, in the form of sulphide of iron. Despite this, iron is still a watchword in the treatment of anemia, and the development of our information regarding hemoglobin as a substitute for other forms of iron has shown that it is a remarkable remedy and superior to the long list of iron preparations, both in and out of the pharmacopeias. Our practical knowledge of the clinical value of hemoglobin preparations is largely the result of clinical experiences of Hayem, Dujardin-Beaumetz and Simon, three eminent Frenchmen, and there is ample literature upon the subject.

Castellino's Clinical Conclusions. The following conclusions have been set down in a comprehensive study of this subject, which was published a number of years ago by Castellino. They still apply with equal force today:

"The absorption of hemoglobin is brought about very

rapidly. It is well tolerated, even in subjects suffering from digestive difficulties, and never produces phenomena of intolerance, such as vomiting, constipation, epigastric discomfort, pyrosis, etc. Its favorable action upon the reconstitution of the blood is shown in the increase of the number of red cells, of their resistance, weight, color, diameter, and their capacity to attain a normal appearance.

"Under the influence of hemoglobin therapy, the general health is benefited, the appetite is increased, the nutrition is better, and there is an increase in weight and strength, with a simultaneous disappearance of the various subjective phenomena of anemia. In cases of secondary anemia, as in cancer, leukemia, etc., there is a benefit obtainable from the use of hemoglobin, but the result is transitory.

"Hemoglobin is indicated especially in those cases of anemia in which there are serious digestive disturbances and malnutrition, as well as in convalescence following febrile disorders and chronic disease. In order to secure the most satisfactory results, it is advisable to give a minimum daily dose of 20 centigrams. The therapeutic indications may be given: Post-hemorrhagic anemia, metrorrhagia, anemias of infectious origin, chlorosis, tuberculosis in a special manner, chronic forms of paludism, and, above all, in conditions of an acute character where there is a marked destruction of the red cells."

The Routine Value of Hemoglobin. From the above remarks, it will be clear that hemoglobin indeed has a place in the routine practice of medicine, for it is a proteid-iron molecule that is easily assimilable and non-constipating. It is the most satisfactory form of iron available in therapeutics and is used and recommended as a rational substitute for various better known preparations of iron, and repeatedly has been claimed to be unsurpassed for the administration of iron by mouth.

Personally, I am inclined to believe that hypodermic injections of cacodylate of iron may be a better hematinic measure in the so-called "acute anemias"—those rapidly developed conditions of anemia due to various toxic and nutritional derangements. In such cases, however, the injections properly may be supplemented by hemoglobin, which is a much more convenient remedy in conditions where hypodermics are not acceptable and, especially, where the anemia is not sudden nor so immediately serious.

According to Potter (Materia Medica, 13th Ed.), "the action of iron is to cause an increase of the hemoglobin of

the red blood corpuscles, either by its direct conversion into an ingredient of hemoglobin or by stimulating the functional activity of the hemopoietic organs, or perhaps by both means combined. This power of enriching the red blood corpuscles by hemoglobin is essentially the whole constitutional action of iron."

Naturally it was presumed by those who were interested in hemoglobin as a remedy of prospective merit, that it would be immediately absorbed as such and be available directly and, as in the case in all "new remedies," these statements were immediately denied. Much bandying back and forth of words ensued in French literature, and, after a number of years, Paul Carnot, now Professor of Therapeutics in the University of Paris, remarked in his book "Opothérapie" (page 92), that "the clinical results appear in some degree to be in contradiction to the theoretical objections which we have just formulated." In other words, whether hemoglobin is digested and changed or not, or whether it gets into the red cell with slight modification, is a technical matter which does not enter into consideration when clinical results are definitely obtained, and hemoglobin, without a doubt, is one of the best forms of organic iron obtainable.

A Broader Therapeutic Effect. It is believed that hemoglobin represents not merely a good means of administering organic iron for its ferruginous value, but according to several observers, hemoglobin actually exerts a homostimulant effect comparable with the effects of other organotherapeutic products, i. e., it definitely stimulates the hemopoietic organs, just as thyroid extract stimulates the thyroid gland or adrenal substance stimulates the adrenals. This may or may not be the case; but it has been proved time and again that iron in the form of hemoglobin is not so quickly eliminated from the body as other organic forms of iron, which, of course, are superior to the mineral forms of which the ferrous carbonate mass is the type.

It is claimed by some investigators that the eosinophile count is an index of the regenerative capacity of the organism and especially of the medullary substance of the long bones where red-cell production has its chief seat. With this in mind, it is interesting to note that Metzner found the eosinophile count nearly two and a half times as great in a series of hemoglobin-fed animals as compared with several controls. Certainly in simple anemias, as well as in chlorosis and secondary anemias in lesser degree, the

hemoglobin index is decidedly raised following a course of hemoglobin by mouth.

Hemoglobin with Synergists. Among the earliest special experimental formulas made in this laboratory was a preparation containing hemoglobin and spleen, and one of the most interesting reports that has ever come to me followed the use of this formula in a case of anemia in an Oakland hospital. The hemoglobin figure was as low as 15 per cent. (Dare) and the red cell count between 700,000 and 800,000 per cu. mm. Naturally there was a loud hemic murmur and a considerable chance that the heart would give out, so suitable stimulation was given for this as well as the special hemoglobin formula. To make a story which lasted several weeks occupy only a few lines, the patient was discharged with a hemoglobin index of 75 per cent., and the red cell count was 4,500,000. After a good many experiments, we hit upon the stock formula which we call No. 13, *Hemoglobin Co.* (*Harrower*), each dose of which represents 6 grains of a mixture containing 4 grains of repurified desiccated hemoglobin from the blood of the steer, 1 grain of desiccated spleen substance and ½ grain of nucleinic acid. The repurified hemoglobin is reinforced by the addition of nucleinic acid (nuclein) and spleen substance, for several good reasons. First of all, iron does not have any special effect upon leucocytosis. Blaud's mass will not affect the white cell count, nor, for that matter, will hemoglobin; but nuclein (originally prepared from the thymus) is the most remarkable stimulant of leucocytic activity known and is used in conditions where an enhanced white cell service would be acceptable. There are many reports of its value, and many of them draw attention to the noticeable resistance-increasing effects of nuclein. It fits in splendidly with hemoglobin, and to my mind the combination is made still better by adding a suitable dose of spleen substance, since this product exerts a good influence in practically all the forms of anemia.

Hemoglobin Co. (*Harrower*) may be given in doses of four to six a day, after meals. It is a sensible, reconstructive treatment in post-operative, post-febrile and post-partum conditions, and is suggested as a routine prescription in all anemias where the first thought is "iron."

A number of physicians have desired to combine the adrenal-supportive formula, *Adreno-Spermin Co.*, with hemoglobin so that it would be better suited for those asthenic individuals whose difficulties are aggravated by anemia and

an associated nutritional factor. For such, the No. 68, *Spermin-Hemoglobin Co.* (*Harrower*), is suggested, since it combines these measures in a very satisfactory manner.

A preparation like this combines several purely physiological stimulative effects, all of which are especially needed following any severe illness whether acute or chronic, in young or old. This will be found far superior because more rational than the old-fashioned tonics like Beef, Iron and Wine, or I. Q. & S., and it will augment the reëstablishment of those essential functions which have suffered from the fever and toxemia from which the patient is convalescing.

SECTION V. CHAPTER 15

REDUCING HIGH BLOOD PRESSURE

Undoubtedly the endocrine glands are related to certain functional disturbances of the arterial tension. While it is still true that the problem of the control of hypertension is a complex one, involving several factors which cannot be considered here, the fog of years is lifting, and clinical experience is showing us the real facts in this case. It is just as obvious that the two distinct types of increased blood-pressure—functional and organic—offer two very different therapeutic problems. Individuals with a functional hypertension are suffering from more or less temporary physiological derangements resulting, among other things, from conditions which irritate or unduly stimulate the so-called "pressor mechanism," while in the other class, mechanical or anatomical factors are involved and there is almost invariably some real pathology. It should be clear that an individual with arteriosclerosis, renal impermeability, cardiac hypertrophy, and other structural changes, would not be in the same category with an individual whose thyroid was inactive or whose adrenal system was overdriven, and naturally, the prospects in the treatment of such organic cases are not nearly so good.

Organic Functional Forms. The tendency has leaned to the study of these organic forms of high blood-pressure, though, in point of fact, the more easily modified functional conditions are much more common. Recently a prominent Dutch internist said that we have no grounds for the assumption that high blood-pressure is always secondary to

heart, kidney or vascular disease. It has no more significance than the discovery of a sclerosis or hardening of a normally soft organ. He continues: "Because we can measure the blood-pressure, we have paid too much attention to it and hidden our ignorance behind the term 'essential hypertension.' The rise in blood-pressure is merely one element of a morbid series which have to be regarded as a whole."

I propose to discuss this matter briefly and essentially from the standpoint of the general practitioner, and especially from the aspects of the endocrine causes and the organotherapeutic treatment.

From the every-day standpoint, there are, as stated, two distinct types of increased blood-pressure, i. e., functional and organic. Individuals with the former have a high tension as a result of temporary or permanent conditions which irritate or unduly stimulate the organs whose function it is to control the mechanism of the circulation. In the other class, the tension may not be so high, but the patients are found to be suffering from arteriosclerosis, renal disease, cardiac hypertrophy and other structural changes which may be both the cause and effect of the increased tension.

There are several classifications of disorders in which changes are prominent in the blood pressure. For the moment we are not interested in these. If, however, one classifies the hypertensives into the two general categories just mentioned, the functional must be considered as the result of disordered chemistry and may respond to well-directed efforts to modify this; while the organic, which are, generally speaking, only amenable to palliative treatment calculated to antagonize incidental factors rather than actually soften the vessels, reduce the size of the heart and bring about structural changes for the better, have a similar etiology but are further advanced.

Overstimulation of the Adrenals. Functional hypertension many times may be due to a temporary overstimulation of the adrenal glands. Despite an occasional statement to the contrary, the consensus of opinion places the adrenal glands in the position of exerting a very definite control over the muscular tonicity of the vascular mechanism and, consequently, of the arterial pressure. In addition to a good deal of experimental data, there has been much clinical evidence to show that factors which stimulate the adrenals first increase their blood-pressure-raising capacity, and, when these glands have become overstimulated

and played out, reduce this factor and consequently permit a subnormal systolic pressure. In view of this, the treatment of this form of high blood-pressure should involve the removal of as many of these adrenal irritating factors as possible, as well as the physiological antagonizing of a hyperfunctioning adrenal system.

According to Louis Klein, (*Therap. Notes,* May, 1921) the hormone of the adrenal medulla—adrenin—controls the contraction of the blood-vessels. A corollary of this proposition is that the presence of high blood-pressure may indicate adrenal hypersecretion. In the study of a case of hypertension without cardiovascular or renal foundation, the logical procedure is to determine which glands, if any, have become sufficiently abnormal to derange the endocrine chain and thus cause the adrenals to put out an actually or relatively excessive amount of their principle. The solution of this problem may not always be easy, but, once arrived at, it repays the student for his efforts. The glands most frequently at fault are the thyroid, the pituitary and the gonads. According to this writer, "Occasionally the etiological factor is an uncomplicated hyperadrenia."

Treatment for Excessive Adrenal Functioning. To modify successfully an excessive adrenal functioning, first remove all infectious foci or sources of toxemia, thus lessening the irritating character of the blood as it passes through the adrenals.

Second, if, indeed, others of the glands of internal secretion, because of some abnormal relationship, are causing an irritation of the adrenal system, this dyscrinism deserves to be studied and modified as best we may be able. Finally, since it has been definitely determined that the pancreas and the adrenals are antagonists, any hyperadrenia would involve either a lessened pancreatic function or encourage us to increase pancreatic function so that the antihormone produced in the Langerhansian cells of the pancreas might be increased in the expectation of overruling at least a part of the excessive adrenalism. It is presumed by many investigators that diabetes is a condition due to a deficient internal secretion of the pancreas, and since von Noorden has called this "the brake to the sugar mechanism," many times individuals with pancreatic insufficiency have an associated hyperadrenia with an unusually sensitive sympathetic system, glycosuria, and also a functional high blood-pressure. Obviously, the treatment of these cases, in addition to such indicated regulation of diet and hygiene, is

the encouragement of the pancreas gland, which can be done very satisfactorily by the use of certain pancreas preparations.

The Endocrine Side of Hypertension. Not a few internists now give routine consideration to the endocrine glands in their study of these cases, while ten years ago they were hardly given a thought.

Functional hypertension many times is traceable to some disorder, usually of a toxic character, which is affecting the production of the internal secretions. For instance, adrenal irritability is certainly a prolific cause of hypertension. Then again, there is an ovarian form which is due to or associated with the menopause; and this is one of the best-known forms of functional hypertension—the so-called "post-climacteric hypertension."

The conviction is rapidly growing that ductless glandular dysfunction is responsible for a majority of these purely functional cases; and, therefore, that their consideration from this standpoint may be the beginning of a successful therapy. Are not the adrenal glands (and the endocrine glands which coöperate with them) charged with the control of the sympathetic system, and, particularly, with the regulation of the cardio-vascular functions? Should they not, then, receive full consideration in the clinical investigation of abnormal conditions in blood pressure, whether high or low?

A persistently low blood-pressure directs attention to the adrenals, and progressive students of clinical medicine think at once of Addison's disease or the less serious form of functional hypoadrenia when a systolic tension of 100 mm. or below is encountered. But as yet we have not given sufficient thought to these glands as causes of high blood-pressure, though undoubtedly increased adrenal functioning is as capable of causing it as hypoadrenia is a cause of the opposite.

We are accustomed to get immediate and lasting results from the use of pluriglandular therapy in cases of hypotension. Why not apply the same fundamental principles in the opposite condition?

Neutralizing Endocrine Irritability. Many students of endocrinology have long realized the comparatively greater difficulty of controlling conditions of hypercrinism than hypocrinism, i. e., of reducing excessive endocrine activity as compared with stimulating or augmenting deficient gland function. Just as the control of hyperthyroidism is more

difficult than the control of hypothyroidism, so it is a more difficult proposition to reduce blood-pressure of internal secretory origin than it is to raise it. However, we do not fold our hands in the organotherapeutic treatment of hyperthyroidism, and really find much good in suitable gland extracts (see Chapter 6 of this section); and I urge that we investigate further the possibilities of the use of "antagonistic hormones" when we have to control the form of high blood-pressure, which is beginning to be believed, and rightly so, to be the result of hypercrinism. Here the increased adrenal function, the abnormal sympathetic irritability and the conditions that go with these states, may be amenable to organotherapy; and there has accrued much advantage, in some cases at least, in carefully applying what little we know of the subject.

Heretofore our therapeutic efforts have been largely limited to the removal of all forms of toxemia — intestinal, dietetic and focal—and this is preëminently right, for the purins, the toxic protein wastes of amino-acid nature, and the poisons that we love to swallow (caffeine, for instance), must be rigidly eliminated. Parenthetically, I must mention the occasional seemingly proper foodstuffs which, because of idiosyncrasy or "protein-sensitization," cause more or less serious chemical reactions in the body. These should be found out and their use stopped. All these poisonous substances must be disposed of by solution and elimination, by neutralization or by well-advised prescribing by the physician, because they are adrenal irritants, and thus keep up a continual stimulation of the blood-pressure control.

Attention also should be called to the emotional causes of adrenal irritability which have been brought to our notice by Prof. Walter B. Cannon's discoveries, which indicate that there is a relationship between emotional stimuli and adrenal excitation. How many times has worry aggravated a case of hypertension? How many times have we seen blood-pressure changes as a result of severe grief or shock?

So we routinely detoxicate, we neutralize, we starve within reason, we purge as much as we dare; and we accomplish something, for the pressure may drop, sometimes quite encouragingly. We have removed a part of the cause, and the adrenals have a better chance to resume their normal service. Why not go a step further and assist in the reestablishment of the disturbed hormone balance? May this not be done by increasing those hormones which are known to antagonize the adrenals? This seems eminently rational.

Sometimes our prophylactic treatment just outlined causes the pressure to drop a notch or two and it may hover around, say, 180 or 190 mm. The regimen becomes a bit too strenuous, or too monotonous, the patient tires of the diet, the medicine and the other treatment, and the pressure begins to increase again. It is here that organotherapy may render the most efficient service.

Pancreas Gland a Remedy for Hypertension. Pancreas substance—the total gland, including the internal secretory cells in the tail and the acinous portion—is an anti-adrenal remedy, and there are a number of references in the literature, especially in that published in Italy, indicating that the pancreas treatment of functional hypertension has been successful in certain cases, and, as we will shortly see, it may be enhanced materially by associating it with other coöperative endocrine products.

Great emphasis must be laid upon the necessity for controlling factors which keep up a continual irritation of the adrenals. It is absurd to expect that physiologic antagonism to hyperadrenia will suffice. Every factor likely to irritate the adrenal glands, including all the matters mentioned elsewhere, should be regulated simultaneously, and pancreas therapy must be considered only as an associated coöperative therapeutic factor.

My own view is that pancreatic organotherapy favors the control of functional hypertension, both by increasing intestinal digestion as a result of its effect upon the pancreatic external secretion, and by its direct anti-adrenal action so well described in the literature and so often proved by experiment and clinical application. This is due to the homostimulant effect on the internal secretory capacity of the pancreas, which has as two of its responsibilities the balancing of the adrenal medullary principle and the regulation of carbohydrate metabolism. Parenthetically, this reminds us of the relation of pancreatic diabetes to hypertension and the condition of adrenal sensitization (shown up by Loewi's test) in hyperadrenia or reduced pancreatic endocrine activity; but this is too large a subject for consideration here. It is mentioned again in Section IV, Chapters 11 and 12.

To repeat: The pancreas very definitely opposes the adrenals; and several authors have spoken well of the depressor virtues of pancreas organotherapy. We, therefore, will attempt to increase pancreatic activity as best we may, and will hope to see results which show that adrenal hyperactivity is being reduced. Often the hypertension accompany-

ing this condition is reduced in a salutary manner, and a diminution of 40 to 60 millimeters is no uncommon thing.

Influence of Gonads on Blood Pressure. The sex glands or gonads, especially the ovaries, exert some subtle influence upon factors which, when uncontrolled, cause changes in the blood-pressure. This seems to be particularly true in women at the change of life. The character of the high blood-pressure, and especially of its response to the regulation of disturbed endocrine function at this period, has caused many pleasing changes in an abnormal systolic tension, which confirm its essentially functional character as well as its responsiveness to suitable organotherapy. The normal decline of gonad function in both sexes evidently is compensated for by a readjustment in other endocrine organs and is quite commonly connected with hypertension. When these readjustments are not made as thoroughly or as quickly as they should be, symptoms of the imbalance soon make their appearance, and again we find an involvement of the adrenal mechanism. Undoubtedly there is an intimate connection between the adrenals and the gonads, with not merely a functional hypertension, but other evidences of adrenal disturbance. Carey Culbertson, of Chicago, (*Surg. Gyn. & Obs.*, Dec., 1916, xxiii, 667), K. I. Sanes, of Pittsburg, (*Am. Jour. Obs.*, Jan., 1916, xxix, 7), and others, have stated in no uncertain terms that the instability of the pressor mechanism at the menopause is connected definitely with ovarian insufficiency, and ovarian therapy has been efficacious in modifying the excessive systolic pressure in these cases. Cummings, of Los Angeles (*Calif. St. Jour. Med.*, 1919, xvii, 373), is also convinced that increased blood-pressure, hot flushes and other circulatory and nervous manifestations at the menopause, are definitely endocrine in origin. In addition to the bromides, he recommends various endocrine extracts for their favorable influence upon functional hypertension of this type.

It has been repeatedly stated that a part of the service rendered to the organism by the sex hormones relates to intracellular oxidation. Hence, the functional recession of gonad activity naturally would tend to favor deficient metabolism and, consequently, a toxemia which must be just as irritating to the adrenals as any other form of toxemia such as has been referred to above.

Ovarian Dysfunction—a Cause of Hypertension. Attention has been called to the frequency with which a high

tension may follow the menopause. There are several interesting reports of the value of ovarian organotherapy in hypertension of this type. Most comprehensive among these is the paper by Carey Culbertson, already mentioned, in which it is shown that vasomotor disturbances of the menopause are largely endocrine in origin—due to the withdrawal of the ovarian hormone and the discord which necessarily results for a time. These regulations and the results from the dominance of this secretion, or that, are gone into in detail in Culbertson's article. Hypertension is the rule in these cases; in fact, it was present in all but four of the whole series which he reported. The fundamental cause is believed by Culbertson to be adrenal hyperactivity and, perhaps, a disturbance of the pituitary following the removal of the influences undoubtedly due to ovarian endocrine function. Based upon this idea, ovarian or luteal homostimulation should tend to neutralize these pressor substances, thereby reducing the tension, and this seems to be the case, since Culbertson reports good results in many such cases.

Sanes, of Pittsburgh (*Trans. A, Gyn. Assn.*, 1918), discussing vasomotor instability at the menopause, also speaks well of the organotherapeutic regulation of hypertension.

The Regulative Effect of the Ovarian Hormone. In this connection an editorial which appeared in the *Journal of the American Medical Association* of Nov. 27, 1920, already published in some of our literature, and which we reproduce again below, lends especial emphasis to the importance of ovarian dysfunction as a cause of functional high blood-pressure, and there can be no doubt that it is possible, by means of suitable organotherapy, to bring down dangerously high blood-pressure without harm to the patient and without recourse to what we usually call "drug action." Here it is:

"It has long been realized that age is a factor which must be taken into consideration in giving an answer as to what constitutes the normal arterial blood-pressure. There are also variations that seem to be associated with sex. In examining the numerous data collected by Alvarez at the University of California, it appears that women before the menopause represent almost exclusively a type endowed with a comparatively low blood-pressure. There is far greater uniformity and less variation in the blood-pressure readings of large numbers of them than is true of men at the same periods of life. Alvarez (*Arch. Int. Med.*, October, 1920) has, therefore, suggested that perhaps the ovary is in some

way able 'to cover up or hold latent the tendency to hypertension which we will presume the women inherit equally with the men.' When the ovarian function fails, therefore, the natural tendency for the appearance of higher arterial pressures soon makes itself appreciated. Perhaps this hypothesis will help to explain the assertion sometimes made that hypertension often develops early in women who show signs of insufficient ovarian function, such as scanty and painful menstruation, sexual anesthesia, male distribution of body hair, infantile uterus, etc. At any rate, the phenomea of hypertension appear to be suppressed in women as long as the ovaries function well. On the other hand, the statistics show that the large increase in the incidence of hypertension comes ten years later in men than in women. Apparently, Alvarez concludes, a strenuous life has less to do with this disease than has the quieting down of the sexual functions."

Placenta—A Pituitary Antagonist. In reply to a recent question put to me as to whether placental extract is useful in high blood pressure at the menopause, I stated that while this substance had been used experimentally by a number of physicians for treatment of high blood-pressure, I did not feel that I could answer affirmatively, as I could not speak from actual experience. Klein, of Detroit, in a recent paper states: "Many endocrine high blood pressure cases are ascribable to some change in the function of the pituitary. We know, of course, how an excess of pituitary secretion might operate in raising the tension. These cases are easily recognized because they frequently have an associated glycosuria due to the low sugar tolerance. The specific antagonist of the pituitary is the placenta." He then proceeds to recommend a desiccation of placenta substance, 5 grains three times a day, for men as well as women, and states that "It meets this indication." Bandler, of New York, too, in his recent book "The Endocrines," makes the following statement: "Placental extract some day may be used to inhibit, if possible, the post-pituitary. The placenta, which is probably responsible for the toxemia of pregnancy, is developed partly from the spermatozoa contributed by the partner. This condition, therefore, may possibly be allied to anaphylaxis." And, of course, it is known that anaphylaxis—or protein sensitization—is a factor in causing functional high blood pressure. None of these last-mentioned conditions, however, are definitely related to the menopause, which, after all, is what was uppermost in my correspon-

dent's mind in framing his question. In this connection my remarks under the heading "The Pluriglandular Treatment of Hypertension" should be noted. There is much to be done in the lines of experimental organotherapy. Some of our friends say that it is improper to acquire some idea from an article, or statement, and test it on a patient. Is it not equally improper, however, to deny to a person a possible benefit from a certain method of treatment which may have been tried many, many times before, merely because you are not thoroughly acquainted with it and able to use it "scientifically"? At all events, I can safely say that many hundreds of physicians have used *Thyro-Pancreas Co. with Ovary* in women with functional high blood-pressure, and especially in that particular kind of hypertension which accompanies the menopause. In men, a similar preparation, containing spermin instead of ovary, is used with comparatively good results. The dose of either of these preparations is one at each meal, and at bedtime, continued for a minimum of three months.

The Detoxicating Influence of the Thyroid. Another important phase of this very large subject must be mentioned ever so briefly. The thyroid is concerned chiefly in the control of the detoxicating mechanism of the body. It is the great oxidizing agent; and when its work is below par (as one would expect it to be in individuals who suffer from the functional hypertension under discussion), conditions favorable to the production of high blood-pressure are allowed to establish themselves. This gives us a partial explanation of the good results reported in some cases of hypertension which have been treated with thyroid extracts alone. In such cases, small doses of thyroid may be given with advantage for months, and the "deaminizing" effect of the thyroid hormone, explained by Slosse, of Brussels, undoubtedly is helpful.

The Thyroid Gland and Metabolism. The thyroid gland is largely responsible for the processes of metabolism, and, consequently, when it is functionally inefficient there may ensue an accumulation of wastes which serve in a mechanical way to raise the blood-pressure. Recently, Llewellys Barker, of Baltimore, (*Ohio St. Jour. Med.*, Oct., 1920, xvi, 709), stated that high blood-pressure appears to depend chiefly upon a narrowing of the lumina of the arterioles in the so-called precapillary areas, and that it is first functional and caused by hypertonus of the arterial musculature, but later may assume a partly organic character as a result

of changes in the arteries themselves. Barker believes that different types of chronic hypertension probably represent different changes in the development of the same fundamental process which may advance with varying rapidity and with varied associated involvement of the cardiovascular, renal, cerebral, and other structures in different cases.

Hypothyroidism Causes Cellular Infiltration. There is an especial interest in this connection when one realizes that hypothyroidism uniformly causes a cellular infiltration that is a result of deficient cell chemistry. The accumulation of the wastes causes a swelling of the cells, based upon the physical reasons of osmosis, for it is clear that these solids draw into the cell an increased amount of fluid in order to dissolve them, and the cells become puffed up with their own waste products—just exactly as we see it so decidedly in myxedema, and presumably this takes place just as much in the precapillary areas above referred to as in other parts of the body. So, aside from disturbances in the detoxicated mechanism, due to thyroid insufficiency, there is also this mechanical favoring of a high tension. This seems to be a very good reason why the use of thyroid extract sometimes makes such a change for the better in certain functional high blood-pressures. The consequent enhancement of cellular chemistry, the removal of the accumulating effete materials, and the lessening of this mechanical opposition to circulation in the remote ends of the circulatory mechanism, is, I believe, an important factor in the thyroid aspects of high blood-pressure.

Hypothyroidism, Infiltration and Hypertension. Towards the end of 1920 there appeared in the *Medical Record* a contribution from my pen, entitled "Hypothyroidism, Infiltration and Hypertension." In his letter to me accepting this article for publication, the editor was kind enough to say: "Your conception of the relations between thyroid insufficiency, infiltration and high blood-pressure is brilliant, and I am sure that it is true."

I have often wondered why thyroid so often reduces high blood-pressure, and especially in certain cases, and I am surprised that this particular aspect of the matter was not thought of before. Since the influence of the thyroid gland upon the chemistry of the body is of such paramount importance, it is worth while to consider it in the functional or essential forms of high blood-pressure. The combination of *thyroid*—to antagonize the cellular infiltration and its mechanical obstruction to capillary circulation; *pan-*

creas—to directly neutralize adrenal irritablity (because it has been shown that the pancreas hormone is the physiological antagonist of the chromaffin hormone), and favor a better alimentary condition, thereby lessening the toxemia which irritates the adrenals; and *ovary*—to modify the imbalance so commonly connected with functional high blood-pressure in women, specially at the change of life, is a very valuable, progressive step.

Thyroid Extract Recommended. There are many references in the literature, too, to the therapeutic advantages of thyroid extract in certain forms of essential high blood-pressure, and as Klein puts it, "if the diagnosis is doubtful a few days of thyroid treatment will quickly elicit the desired information." He reports having recently seen three patients, all of whom had a systolic blood-pressure ranging from 180 to 210 mm., who were made perfectly comfortable and whose blood-pressures were reduced below 160 in a short time with no other medication than one-sixth of a grain of thyroid extract three times a day. I want to call special attention to the frequency with which this form of high blood-pressure occurs in patients who are obese. It seems clear to me that these patients are not oxidizing with sufficient rapidity the products of destructive metabolism, and, therefore, because of the deficient stimuli from the thyroid and associated glands, there accumulate certain protein wastes which overburden the emunctories and thereby directly raise arterial tension, not merely from the cause just mentioned but from the direct irritating influence of these products upon the adrenal mechanism previously referred to. Thus the thyroid aspect of functional high blood-pressure is extremely important since the administration of thyroid in suitable cases, in addition to favoring a better chemistry in the manner just suggested, is also an indirect means of antagonizing adrenal irritability and, consequently, is a coöperative measure of considerable value in conjunction with pancreas.

Blood Pressure in Hyperthyroidism. Sir James Barr (*Practitioner*, June, 1921, p. 387), says that in hyperthyroidism the mean arterial pressure is lower than normal owing to lessened peripheral resistance due to dilation of the arterioles and diminished viscosity of the blood. The capillary and venous pressure rise, however, and this leads to a large supply of blood being furnished to the heart, an increased systolic output and a raised systolic pressure; but owing to a low peripheral resistance, there is a great fall in

the pressure gradient with a relatively low diastolic pressure. This combination of high systolic and low diastolic pressure causes longitudinal straining of arteries, and leads to waste of energy, for the heart is overloaded and its energy chiefly expended during systolic and not stored up in the elastic walls of the arteries. In hyperthyroidism there is deficient vascular tone; hence the hypertrophy and dilation of the heart with elongation of arteries often seen in this condition. Adrenal extract, by improving vascular tone is, therefore, valuable in hyperthyroidism. It may here be stated, that this is one of the reasons why *Pancreas Co.* (*Harrower*) contains adrenal substance and is often used with real success in hyperthyroidism.

Importance of the Endocrine Balance. Quite recently in an editorial note in *Clinical Medicine* (December,, 1920) the following statement appears: "Endocrine balance is vital; when it is disturbed the organism is ailing. Does one member of the endocrine chain lag or for any reason fail to function, then another, in the absence of a normal restraint exercised by an opposing gland, renews its efforts with provocative increase of secretion. A striking example of this is given by Bandler (*N. Y. Med. Jour,,* June 5, 1920, cxi, 972). He shows us that the thyroid gland during pregnancy is under a strain in consequence of the extra work it has to do. The same is true during lactation, and occasionally symptoms arise that are referable to an unopposed adrenal action, such as high blood-pressure, flushes, palpitation, nervousness, and so on. The prevention or control of these symptoms is accomplished by thyroid therapy, and Bandler reports excellent results from the administration of small doses of thyroid gland."

Each of these three organotherapeutic measures is especially helpful in the type of cases mentioned. It happens that many of these cases overlap, and it is not overstating things to say that many have all three of these factors simultaneously present. At all events, it is a very common thing to find hypothyroidism at the menopause (it is said that ninety per cent. of all cases of myxedema occur in women and ninety-five per cent. of these occur in women in the decade between forty and fifty!). The hypothyroidism and hypo-ovarism which one expects to find under such circumstances routinely are accompanied by an adrenal irritability for reasons previously mentioned and consequently, as I see it, the treatment of functional high blood-pressure at the change of life is best accomplished by the

addition to the routine detoxicating and regulating measures of a pluriglandular therapy involving the ovaries, the pancreas, and reinforcing these with small doses of thyroid.

Pluriglandular Therapy of Hyperthyroidism. For four years we have been working upon this particular problem, and not merely have I been successful in reducing a number of the functionally high blood-pressures, ranging from 180 to 300 mm., but many of my colleagues have seen fit to follow my suggestions, and the reports which have come to this office prove that this is a rational and advantageous measure. Provided the increased tension is functional, it may be reduced many times in a very encouraging manner by following this method of treatment.

Thyro-Pancreas Compound with *Ovary* (*Harrower*) contains two grains of desiccated total pancreas gland (not pancreatin, two grains of total ovarian substance, and one twelfth of a grain of U. S. P. thyroid. One such dose is given at each meal and at bedtime, or four times a day, for a minimum period of two months and in some instances considerably longer, especially in women where there are other evidences of endocrine imbalance.

In the treatment of functional high blood-pressure in men, a similar preparation is almost as efficacious. This is called *Thyro-Pancreas Co. with Spermin* (*Harrower*). The formula is identical with the one mentioned above, save that the ovarian element is replaced with spermin from the interstitial cells of Leydig. The dosage is also the same.

Both of these pluriglandular formulas have been tested many thousands of times. The aggregate of results has been good, and while many cases have been treated in whom there was really no functional endocrine basis for the high blood-pressure, still the average has sufficed to convince us of the possibilities of this matter. These formulas are well worthy of consideration; since high blood-pressure, whether functional or organic, is a dangerous proposition. I have yet to find any reports of detrimental by-effects. Certainly such measures are more rational than the nitrates or other vasodilating drugs, for it seems that something of a real physiological character is being accomplished by the organotherapy.

Warning Against a Wrong Attitude. It should be emphasized that our consideration of this subject and the treatment of these individuals from the endocrine standpoint always should be a part of a well-regulated regimen. While it is true that certain investigators prefer to regulate their

treatment so that they can acquire definite information as to the responsiveness of the patient to their treatment, or, in other words, to the efficacy of their remedy, I am very much opposed to this attitude in a clinical way, for this reason: I consider that the patient's interests come before my own, that while it would be very interesting to know certain reactions of the patient to a certain line of treatment, and to acquire as much diagnostic information in this way as possible, it is wrong to deny the patient the benefit of whatever may be fundamentally advisable until we are satisfied that a certain measure is good or not as the case may be. In other words, if there is indeed an eliminative aspect to a given case, this should be treated. If the diet needs to be regulated, it should be regulated. If there is an endocrine dysfunction of several ductless glands, they should be treated together and every measure calculated to render service to the individual should be instituted, *and instituted simultaneously,* if possible.

Clinical Results from this Method. Some of the results have been most encouraging. From my own records, I can give several figures: A woman of 50 came with a B. P. (systolic) of 245. After one month it was 190 and after two months it was 172. She has evidently much improved. Another woman at the menopause took the capsules (S. F. No. 30) for about a month; the tension was reduced from 185 mm. to 155 mm. A gentleman followed my suggestion for less than a month, i. e., he cut out coffee, took an alophen pill every other night (on general principles) and the S. F. No. 29 q. i. d. His tension was reduced from 185-190 mm. to 140 mm. Still another case, using the same formula, showed a reduction of 40 points when the seemingly irreducible minimum was 190 mm. Many reports have been made to me personally and by letter. I can mention a few of these figures off-hand: 210-160; 180-135; 200-145; 185-140; and 220-175. All these figures refer to the systolic pressure, for it happens that functional high blood-pressure usually concerns more the systolic than the diastolic figures.

We cannot definitely promise any uniform results from the treatment, for the value of this method depends a great deal upon the conditions present and, especially, the responsiveness of the endocrine glands. The *raison d'être* is quite logical, and the percentage of results is high enough to raise our hopes. It is a measure which to my way of thinking far outclasses the nitrites, iodides and other half-way measures routinely used in this common condition.

Conclusions. To conclude this study, and to sum up:

1. Certain functional hypertensive conditions deserve to be considered from the standpoint of endocrinology.
2. These cases should be carefully selected and the organic factors eliminated.
3. After as thorough detoxication and elimination as is possible to secure, and in conjunction with this treatment and preventive, dietetic and hygienic measures, I suggest organotherapy.
4. Pancreas substance is indicated. Thyroid is eminently useful. Ovary is of decided value in certain cases. Pluriglandular therapy has a reasonable basis and is worthy of a trial.

The whole subject of the treatment of functional high blood-pressure has been revolutionized by the development of organotherapy, and particularly pluriglandular therapy. Many patrons of The Harrower Laboratory and correspondents of mine have written enthusiastic statements in regard to the splendid reductions in blood-pressure that have followed this method of treatment, and for this reason *Thyro-Pancreas Co. with Ovary* (*Harrower*), (or *with Spermin*, as the case may be) is confidently recommended. The usual dose is one at each meal and on retiring. Treatment should be kept up for at least three months.

SECTION V. CHAPTER 16

ORGANOTHERAPY IN ASTHMA

During the three years that we have been experimenting with various organotherapeutic preparations in the treatment of various forms of asthma I have felt that of all the possibilities of results from this type of treatment, the results in asthma were least dependable. Unfortunately, asthma is a very complicated condition, and cases that appear to be similar to one another in manifestations really differ materially in their origin. In all references to the pluriglandular formula that we have developed for the treatment of asthmatic patients we have emphasized the fact that it was experimental. It is a good remedy in the right kind of cases, and it is practically impossible to determine which cases are in this category until the remedy has been applied for two or three months. Most of the individuals

who have taken *Adreno-Hypophysis Co.* (*Harrower*), as well as their physicians, have adopted it in despair, since they already had tried many measures and had failed. Naturally, this class of cases is less likely to respond to any kind of treatment than more simple ones in which the fundamentals are not so complex, and in spite of this we have had a fairly good percentage of results.

An Experimental Measure. I still feel that this method of treating asthma is, as already stated, experimental, because the fact that various food proteins cause asthma in suitable individuals; that certain pollens and other similar substances may cause manifestations akin to asthma; and, then, because most of the patients that have bronchial asthma have bronchitis with it, and there is an absorption from the focus of infection of a considerable amount of the bacteria protein products to which the patient undoubtedly is susceptible, make the prospects very indeterminate.

The symptoms of asthma have some similarity to those connected with endocrine disturbance, and for some years it has been shown that the distressing paroxysms usually can be promptly controlled by injections of from 3 to 10 minims of adrenal chlorid solution, 1:1000. Unfortunately, the effects are ephemeral, and sometimes an effective dose of adrenalin causes a temporary vasomotor spasm which is quite uncomfortable. More recently there have been a number of reports referring to a combination of the adrenal and posterior pituitary solutions by hypodermic injection instead of adrenalin alone, and it is believed that the effects of this combination are more far-reaching and lasting. It is well known that such treatment is only symptomatic and, of course, it is inconvenient, and quite a number of physicians have presumed that the prolonged administration of some of the products of this character by mouth might be successful likewise. The subject is still in the experimental stage, and it is hard to say anything very definite about it.

The Endocrine Aspect of Asthma. Selfridge, of San Francisco, has been working on this subject for some years and recently published an article in the *California State Journal of Medicine* (April and May, 1919), reporting the endocrine findings in a number of cases of asthma. These seem to indicate that dyscrinism is an underlying, causative factor and that the control of disorders of this kind simultaneously may favor the control of the asthmatic attacks. Selfridge concludes his paper with some remarks worth

quoting here: "The question of the ductless glands has been brought forward because we cannot see all cases, belonging to the different groups mentioned, cured entirely by the removal of focal infections plus the injection of various protein solutions. And, while we admit that very many cases may not be benefited by the administration of gland products by mouth, especially in adults, we feel that the recognition of gland deficiency among children particularly, who exhibit vasomotor ataxia and in whom these suggestions as to treatment are followed out, may ultimately enable us to put into the class of cured cases those who otherwise might be doomed to grow up as defectives."

Anterior Pituitary Substance in Bronchial Asthma. A series of clinical experiments which may be of much practical value were carried out by Frederick Warfel in the Indianapolis City Hospital (*Indianapolis Med. Jour.*, July, 1915) to investigate the possibilities of organotherapy in bronchial asthma. While the administration of anterior pituitary substance in this condition was and still is empirical, it is well known that this extract has encouraging results in certain developmental disorders and irregularities of metabolism in which the endocrine organs, and especially the pituitary gland, are concerned.

Since the paroxysms of asthma are frequently controlled in a remarkable manner by injections of adrenalin, Warfel wondered if there might not be a definite hypoadrenia which could be modified by organotherapy. He proposed to do this by recourse to one of the peculiar phases of organotherapy —the use of extracts from an organ or organs which indirectly increase the physiologic activities of a hormone-producing organ which is in intimate relation to the organs from which the extracts are made. Incidentally it might be remarked that adrenal insufficiency is frequently benefited by certain glandular extracts or combinations of extracts other than adrenal substance itself.

Warfel selected seven cases of bronchial asthma, as nearly typical as possible, and to each gave 2½ grains of the desiccated anterior lobe substance four times a day. His article contains a report of each of these cases, and the conclusions drawn seem to indicate that his treatment offers much encouragement in the control of a condition which is not easily influenced by other therapeutic procedures. He reports that each case thus treated showed a marked improvement in the prominent symptoms within 48 hours. The treatment was continued for periods ranging from ten days to seven

weeks, with most encouraging results. The expectoration was decreased, a circumstance which was accompanied by a feeling of dryness in the mouth and throat which, however, was relieved by sipping water. The distressing dyspnea disappeared entirely. In two of the seven cases there was a considerable trace of albumin in the urine which disappeared after the treatment had been continued for a short time. The blood pressure did not seem to be influenced either up or down; and Warfel, while admitting that the number of cases was limited, suggests that as the results secured in this series were so generally favorable and constant, further trials of this procedure are desirable in other similar cases. Since the publication of his first report, many additional cases of bronchial asthma have been treated as outlined above, with good results. It seems to be a measure worth trying still further.

The Complexity of the Asthmatic Syndrome. The trouble with the problem of the asthmatic is due to the fact that bronchial asthma is a very complex condition. There is an undoubted endocrine factor in many cases, but too often there is a bronchitis with absorption of the products of bacterial growth and decomposition, with an anaphylaxis-like reaction to these foreign proteids. Again, similar reactions occurring in unusually sensitive persons following the absorption of protein from pollens and other similar substances—hay fever, horse asthma, rose colds and such like—are a few of the manifestations of this character which complicate matters. The majority of individuals suffering from bronchial asthma are asthenic, and there are not a few references in the literature to the value of adrenal substance in cases of this kind; it might, therefore, properly be included with anterior pituitary substance in an antiasthmatic pluriglandular formula. Based upon these scattered notions, a number of experimental formulas have been made and used in different kinds of asthma with varying results. In fact, in some instances, the results were very good, while in a number of others they are quite negative.

An Organotherapeutic Formula. A number of suggestions along these lines have been carried out in this laboratory, and a formula (No. 26), *Adreno-Hypophysis Co. (Harrower)*, is offered for use in the various phases of asthma in which the effects likely to be secured from a formula of this kind possibly might be of adjuvant value in the treatment.

There are several suggestions in the literature that calcium lactate has been beneficial in certain asthmatic states, and this salt is therefore used in the excipient.

Since bronchial asthma, especially in elderly persons, is such a heart-breaking condition and so unresponsive to ordinary treatment, save only the hypodermic injections which most asthmatics soon come to dread, it really seems as though experimental glandular feeding should be more routinely suggested. While there is no way of telling in advance what sort of a result may be secured, it may be stated definitely that the administration of the average doses of these glands is without harm, and on an entirely different basis from the continued injections of the adrenal or pituitary principles.

The administration of *Adreno-Hypophysis Co.* should be carried out with a full understanding on the part of the patient that it may or may not be of service. We can speak with confidence of the value of the adrenal support obtained from that particular ingredient, and this, of course, is worth while. We can tell what others have said and of results that have been secured, but the subject is being discussed here with some diffidence merely because there is so much yet to be learned. The dose recommended is from three to six doses a day, and obviously every effort should be made simultaneously either to control any infective condition that may be present or to have the patient keep away from foods and conditions which are known to be aggravating. A reduction of the amount of animal proteids that are eaten and persistent colon hygiene invariably should be recommended.

I want it understood that this whole proposition is purely experimental. We have not a cure for asthma, and I make no pretentious claims to any special knowledge on this subject. We only know that some people who have had asthma for years and "have tried everything else", are now free from it.

It will be a pleasure to coöperate with interested physicians who may have some ideas regarding the development of our present knowledge of asthma from the endocrine standpoint; and it should be remembered that my laboratory was established for the express purpose of broadening practical clinical information, where this is possible, by making a given idea immediately and conveniently utilizable by those who choose to do so.

SECTION V. CHAPTER 17

ORGANOTHERAPY IN NEURITIS

I have run across many cases labeled neuritis that were nothing more or less than irritability of certain sensory nerves, due to toxemia. According to Dorland, neuritis is "inflammation of a nerve" and we shall now proceed, if possible, to connect this condition with disturbed endocrine function.

Every physician knows that the chief cause of neuritis is toxemia. It may be bacterial, and often is, but very much more often it is due to the absorption of poisons either from the alimentary canal, or from foods which are ingested wilfully or accidentally.

Every physician also knows that chronic conditions in which the chemistry of the body has been disturbed by whatever circumstances may be involved, are very commonly associated with painful disturbances that are called neuritis. They may not be technically and scientifically neuritis, but they are called neuritis and the point is that these conditions are due to the accumulation of unoxidized waste products which cause an irritation which produces symptoms exactly similar to those accompanying a real inflammation of the nerve.

The Thyroid Involvement. One of the commonest causes of deficient cellular chemistry is hypothyroidism. Consequently, one of the commonest causes of neuritis is hypothyroidism. We need not take very long to find that this is the case. Myxedema, the most decisive form of full-blown hypothyroidism, practically always is associated with neuritis, and other painful manifestations due to the cellular intoxication and infiltration of the nerve cells and their sheaths, and the discomfort is very real, though, fortunately, amenable to thyroid therapy.

One does not have to look for so serious a thyroid insufficiency as myxedema to find a beginning of the discomforts that ordinarily are called neuritis. Many an individual whose detoxicating mechanism has been overburdened, suddenly finds that an arm, or shoulder, or calf, or some particular locality of the body is very painful and tender, and perhaps there may be even more serious manifestations in the nature of what appear to be a paralysis and motor diffi-

culties. At all events, to repeat, hypothyroidism is very commonly associated with neuritis and, therefore, to my way of thinking, whenever we run across an individual who complains of neuritis, one of the things in our further investigation of these cases is to determine whether their physiological chemistry is as normal as it should be, and, if it is deficient, whether the thyroid possibly is at fault.

Advantage of Harrower's Thyroid Test. I have treated many scores of cases with neuritis: some of them with no other particular symptomatology; others associated with rheumatism, or anemia and the general run-down condition so common in chronic disease, and these cases were treated successfully many a time by considering that they were suffering from hypothyroidism. In many cases I have established my suspicions by the use of my Thyroid Function Test and then have changed from an empirical attitude to a more scientific one; however, in most instances, whether the Thyroid Function Test obviously is an indicator of a hypothyroidism, or whether I merely presume that hypothyroidism is present, I begin to encourage the cellular chemistry, increase the circulation and favor in this manner a return to a more normal condition with the result that in many instances the neuritis has disappeared. I have cured neuritis too often with organotherapy to listen to any who deny this.

Adrenal Depletion is Common. There is another aspect to neuritis that deserves equal mention and consideration. All of the individuals in the class we have been discussing, are of the type that is often called "hypoadrenal." The toxemia, usually of long standing, has overstimulated the adrenal glands until they are physiologically depleted, and in conjunction with the resulting neuritis, we have obvious evidence that nitrogenous elimination is deficient—the urea in twenty-four hours is much below normal, sometimes is 0.9 per cent. or less, and practically always is one half of what is considered to be an average normal percentage of a twenty-four hour specimen. There are plenty of evidences of poor circulation—the skin is sometimes bluish and mottled in appearance, the extremities are cold, the heart action is often weak and the systolic blood-pressure many times is below 100 mm. These patients are just as tired as their chemistry is tired. They have all sorts of aches and pains—sometimes they are cerebral and are in the nature of a chronic persistent headache, many times worse in the mornings—and a neuritis is added to all these other difficulties.

Bearing these things in mind, might we not say that these individuals have a thyro-adrenal insufficiency? They do, as a matter of fact, for many, many times hypothyroidism is complicated by adrenal insufficiency and, on the other hand, the opposite is equally true. These two endocrine glands work together. They regulate the detoxicating mechanisms of the body. They are believed to be concerned in the control of immunity. They involve those factors which stimulate and regulate the sympathetic mechanism of the body. They assist in maintaining the tone of the muscles and also, most important of all, they arouse, or set in motion, the chemical mechanism we call detoxication.

A Routine Treatment of Neuritis. Neuritis, then, is commonly associated with thyro-adrenal insufficiency and an organotherapy directed at encouraging the thyroid activity and antagonizing the circumstances resulting from the adrenal insufficiency, is very likely to modify the neuritis satisfactorily.

Adrenal support is a tried-and-proved measure in neuritis that is based upon a physiological derangement of the endocrine organs under discussion. It is directed at what is often the real underlying cause, and failures in the treatment of neuritis often have been due to ignoring this cause. The use of the formula, *Adreno-Spermin Co.* (*Harrower*) for a month or six weeks, coupled with a purin-free diet and the routine elimination and local measures in customary usage, is as effective a routine as I have run into.

So far as other measures are concerned, besides every effort to reduce toxemia to the utmost, I have found that certain foods including the easily putrefiable proteids and especially certain substances to which individuals are unusually sensitive (food allergy), often are aggravating factors; this aspect should be taken care of at the same time.

Focal infection, the most common cause of adrenal insufficiency, and the syndrome under consideration, should be sought for most carefully, and every effort made to remove it. Many a neuritis of the arm is based upon several bad teeth. Or a tonsillar infection may occur in apparently normal tonsils, in which the crypts only are infected, and in which there is no obvious swelling or anatomical change.

A common basic cause which must not be overlooked is alimentary toxemia. A chronic appendicitis many a time has been the real cause of a serious neuritis. Digestive apathy—both secretory and muscular—and intestinal stasis

are, perhaps, even more important; and the alimentary encouragement offered by *Secretin Co.* (*Harrower*)—see Section V, Chapter 24—has often indirectly helped a bad neuritis.

Remineralization. With this line of treatment, in addition to the use of measures calculated to increase alimentary elimination thoroughly, I urge remineralization or the antagonizing of the accumulation of acid wastes, which result from the disturbed chemistry just referred to. These patients very often are in the condition of systemic acidity or hypoalkalinity which may be as much at the bottom of neuritis as any other factor. *They are starving for alkalies,* and their slow chemistry favors the accumulation all the time of still more acid, which removes from the body its rightful reserve of these all-essential mineral salts. The French many times have referred to the importance of remineralization in conditions of neuritis, and one of the important associate measures which may be given in conjunction with organotherapy, is this remineralization, or the administration of certain suitable alkali salts in the expectation of adding to the reserve of these substances and neutralizing as many as possible of the accumulated wastes as well as those which are being produced from day to day in greater amounts than can be taken care of routinely.

We have a formula called *Calcium-Phosphorus Co.* (*Harrower*) which contains magnesium phosphate, calcium phosphate, calcium glycerophosphate, potassium bicarbonate and sodium bicarbonate, in proportions quite similar to those in which we find the various salts found in the body. Five or six grams a day of such mixture is a very decided advantage in the associate treatment of neuritis. (See chapter on "Remineralization," Section V, Chap. 25.)

The combination of organotherapy mentioned above and remineralizing treatment should be recommended for at least 8 or 10 weeks. The usual dosage is one of the *Adreno-Spermin Co.* at each meal and at bedtime, plus three of the *Calcium-Phosphorus Co.* tablets, crushed, with much water an hour before food twice a day for three or four weeks and thereafter on alternate weeks. This makes up a combined cell-stimulating and waste-neutralizing routine which has had to do with the cure of many scores of cases.

The endocrine side of the treatment of the various forms of neuritis is as encouraging a one as I know of, and literally scores of physicians have expressed themselves as delighted at the application of the foregoing measures.

SECTION V. CHAPTER 18

INTERNAL SECRETIONS IN RHEUMATISM

In June, 1915, the publishers of *American Medicine* (New York) produced a very comprehensive and creditable special issue on rheumatism. The editor kindly invited me to contribute some ideas on the endocrine aspects of this disease, and the following remarks, modified and brought down to date, are passed on for what they may be worth to readers of this book.

Rheumatism and the rheumatic diathesis are conditions concerning which there are numerous and widely differing views. The literature regarding the various phases of rheumatism is as extended as it is contradictory. The unsuspecting reader frequently is led into a morass of differing conceptions from which it is not always the easiest thing to extricate himself.

Ideas Regarding the Causes of Rheumatism. Some writers insist that "rheumatism"—and by that they usually include the varying disorders which have been classed under this name—is a manifestation of digestive trouble pure and simple; correct the digestion and the rheumatism automatically will be taken care of.

Others insist that it is essentially the result of an imperfect mineral metabolism and assure the reader that recourse to certain inorganic neutralizing measures will quickly bring conviction regarding the correctness of this view.

Still others assert that there is a bacterial origin, not only for the obviously infective forms of rheumatism, but for all of them; and that the successful treatment of this disorder is not complete without at least the addition of procedures based upon its "undoubted microbic origin."

Much has been written regarding the relation of uric acid to the rheumatic diathesis, and opinions seem to be veering away from the statements so ably presented by Haig, of London. In a communication which appeared in the *Interstate Med. Jour.*, April 1915, Goodman, of St. Louis, aptly remarks that: "The uric acid theory is at present tottering on its unstable foundations and we are growing more and more inclined to the view that not uric acid, but rather disturbances of intermediary purin metabolism, are at the root of the evil."

The Broader Aspect. Looking at this problem from the standpoint of an average physician, it is altogether probable that there is an element of truth in all of the theories regarding rheumatism and that the statements which serve as a prelude to this article are all correct to a certain degree. None can deny that rheumatism, in the majority of instances, exhibits as one of its most constant manifestations a disturbance of metabolism, and considerable evidence is accruing to indicate that not a few of these cases have as the original basis of the trouble an obscure infective process which may never be so obvious as to direct attention to itself, but is only brought to light following the empiric use of stock vaccines given with the expectation that this unnoticed infection may be present. In such cases (and Sherman, of Detroit, has frequently directed attention to the importance of this class) the diagnosis is often made by the clinical results of the empirical treatment, and it may be stated in unqualified terms that many of the chronic rheumatic affections are of bacterial origin, even though they may show none of the typical findings of obviously infective cases.

An Alimentary Factor. The manifestations of the rheumatic diathesis are too frequently associated with digestive disturbances for the consistent physician to deny the intimacy of this relation, and it is not an uncommon thing for dietetic regulation, with attention to the inevitable defective elimination resulting from digestive activity, to bring about complete control of the rheumatic phenomena. Certain it is that the excessive amounts of proteid which are so commonly eaten combine with other factors to bring about the metabolic chaos which is so usually called rheumatism. Parenthetically, it might be remarked, these persons are not suffering from the results of mineral excess, although the laboratory evidence may seem to indicate this; rather they are undergoing their tortures because of a *lack* of the natural mineral elements—the vegetable alkalies—which the body needs, and which they could just as well have if their diet included more of such articles as potatoes, greens and cereals, and less meat.

Whether or not the initial cause is dietetic or bacterial in origin there can be no doubt that all forms of rheumatism are evidences of essential changes in the chemistry of the body, and, this being granted, should not the regulators of metabolism be considered both in the etiology as well as in the treatment of the various forms of this disorder?

The Internal Secretions in Rheumatism. It should be quite unnecessary to lend emphasis to the importance of the glands of internal secretion as regulators of the functions of the body. The hormones not only control, but correlate these various cell activities, and their work is so closely connected with the factors which are concerned in the reaction of the body to the causes of rheumatism, as well as to the attempts made to remedy this condition, that the physician who considers the relation of the internal secretory glands and their hormones to rheumatism is more likely to solve some of its mysteries than the one who overlooks them entirely.

It is remarkable how close a relationship may be discovered between certain of the ductless glands and the symptoms which have come to be considered pathognomonic of rheumatism. Presuming for a moment that the various manifestations of the rheumatic diathesis are toxic in origin, is not detoxication essentially controlled by certain of the endocrine glands?

If the infective origin of rheumatism is admitted to be the most frequent or important, then we must also admit that certain of these remarkable organs are responsible for the production of the protective measures which the body automatically bring into play in infections. Sir Almroth Wright himself insists that all the substances concerned in the control of infections must be considered as products of the internal secretory organs.

If functional digestive disturbances are the most common basis for this condition, then it is proper to consider the relation of the alimentary hormone, secretin, to this disease and, where digestive insufficiencies are manifestly present, have recourse to the use of secretin as a remedy, for I am thoroughly convinced of its value as a physiologic means of stimulating lazy or inactive digestive glands. So whether rheumatic conditions are purely metabolic in origin, or whether they are due to microörganisms, or to indigestion, we must not belittle the fact that in any event there must be a rôle that the internal secretory organs play which favors their prevention as well as the cure. The clinical use of an alimentary stimulant, such as *Secretin Co.* (*Harrower*), in suitable cases, so modifies the digestive toxemia that an immediate change in the rheumatic manifestations is often noticed.

Under the present circumstances it would be quite difficult to consider this from the protective or prophylactic

standpoint. Rheumatism is too insidious a disease. Its onset is of such a nature that it is not appreciated until one or more of the more definite manifestations—joint pain, immobility, swelling, etc.—brings the patient to his physician. We can, however, make good use of this information in the diagnosis and treatment of rheumatic conditions. For example, too often the orthodox treatment with salicylates or other neutralizing agents, does not give the desired degree of results, or merely tides the patient over whilst the disturbed chemical conditions are under the influence of the drugs or measures used. After a longer or shorter time the patient has a recurrence and unfortunately too often it is more severe than the initial attack. In such cases the knowledge that the ductless glands may be frequently concerned in rheumatism will enable the physician to consider the case from a slightly different angle—one which I regret to say is rarely taken by the medical profession—and this new viewpoint may facilitate the control of future manifestations. It will also open up the possibilities of certain forms of organotherapy which, rightly applied, may materially influence the response of the organism to the other usual therapeutic procedures. Right here it should be emphasized that organotherapy is not recommended as the *sine quâ non* in the treatment of rheumatic affections. Far be it from such, but as an important adjuvant and a phase worthy of consideration it deserves considerably more attention than it has previously received, as may shortly appear.

The Importance of the Thyroid. Léopold Lévi, of Paris, insists that the thyroid is quite intimately connected with both the cause and, in certain cases, the successful treatment of various joint conditions, not excluding the most serious form, arthritis deformans, and in the introduction to his little book (La Petite Insuffisance Thyroïdienne et son Traitement") he makes the following statement: "Therapeutics is invaluable in the study of minor thyroid insufficiency. It has revealed to us a certain number of stigmata of hypothyroidism (which might otherwise be overlooked). In March, 1905, we had applied thyroid treatment, for the first time, aside from myxedema, on a patient affected with chronic rheumatism accompanied by psoriasis. The primary effect produced by the medication was in the nature of the increased appetite. The patient when first questioned as to the effect of the feeding with the thyroid gland, said:

'It makes me ravenous.' Subsequently his appetite was so abnormal that those in attendance on the patient thought he had tenia. A second result following the medication was a marked decrease in the *chilliness* which he had been experiencing. The patient had been chilly to an amazing degree, and in the room, which he occupied, was able to stand a temperature of 73 degrees Fahr., living, moreover, as if rolled up in a glass screen. The effect of the thyroidotherapy was such that he was not so fearful of the cold. Soon he said he no longer needed the screen. At night he had less clothes on the bed, and whereas, he formerly called for several blankets and an eiderdown on his bed, he was now satisfied with one light blanket. Thus the result of thyroid treatment on this first patient was such as to direct attention to the influence exerted by the thyroid gland on the appetite mechanism, as also on the sensation of chilliness. The application of thyroidotherapy to other cases of chronic rheumatism enabled us to recognize the effect of thyroid treatment of *constipation.*"

Elsewhere in the same book the author connects thyroid disturbances with rheumatic manifestations and quotes a large number of reports to the effect that "*the reality of the thyroid causes of chronic rheumatism is incontestable.* its existence depends in many cases on thyroid lesions."

Chronic rheumatism is quite common in subjects presenting signs of hypothyroidism and it is well known that rheumatic manifestations may be associated with or aggravated by incidents in the menopause. Frequently rheumatic manifestations follow thyroid atrophy due to pathological conditions or following thyroidectomy for Graves' disease, but the most important proof is the fact that the use of thyroid extract in many cases ameliorates rheumatic manifestations.

Thyroid Therapy may be applied frequently in the treatment of various forms of arthritis with good results. There are a number of papers recording and attempting to explain its remarkable results in various forms of chronic rheumatism. Probably the most comprehensive of all these communications is that of Léopold Lévi who reports three hundred cases treated under his direction during a period of eight years. This investigator, who is well known to those who have read the literature on the thyroid gland, differentiates a form of rheumatism which is due to what he terms thyroid instability. The disease is found in relat-

ively young persons, is only slightly deforming, and usually affects the smaller joints. It seems to progress by fits and starts. In these cases the joint disturbances are by no means the only troubles. Occasionally there are other manifestations of functional thyroid disorder, sometimes evidently due to increased thyroid activity and at other times, the majority of cases it may be noted, the result of decreased thyroid activity.

The manner in which this form of rheumatism responds to treatment, varies considerably with the associated manifestations. In the juvenile form, where there is no very serious deformity, the response to treatment is good, and while the serious chronic and so-called "incurable" cases do not respond as rapidly to this treatment, there is no doubt that persistent thyroid therapy causes a very decided benefit even in them. Lévi concludes that in many cases of chronic rheumatism thyroid extract is "a valuable remedy," securing an average of results that is very encouraging, and occasionally producing astonishing changes for the better. According to this writer: "Thyroid therapy should be placed in the first rank of the therapeutic armamentarium in the treatment of chronic rheumatism." He recommends a daily amount ranging from .05 to .30 grammes (1 to 5 grains) in divided dosage. The average is 1½ grains a day and it must be continued for as long as six months.

The Philosophy of Thyroid Therapy. The mechanism of the action of thyroid extract in certain conditions has for some time been in doubt; and this is especially true as far as its influence in rheumatism has been concerned. This extract, above all others, has been considered one of the best means of enhancing cell activities and increasing the metabolic exchanges. Since the metabolism in rheumatism is much below par, any advantage that accrues from thyroid therapy might be considered as due to this salutary influence upon the cells. A scientific explanation of this may be gathered from some interesting experiments by Slosse, who was professor of physiology at the University of Brussels before the war. He has carried out a number of experiments both in the laboratory and in the clinic to connect the disturbances of nitrogenous metabolism with the work of the ductless glands, and as a result of his investigations he states that under normal circumstances the thyroid gland secretes a *"hormone de désaminization"*—a deaminizing hormone—which influences the nitrogenous ex-

changes and, when deficient, causes a reduction of the power of the cells throughout the whole organism to split up the albuminoid substances, especially the nucleo-albuminoids, from which uric acid and other substances of the purin group are formed. Theoretically then, the enhancement of thyroid action should favor nitrogenous metabolism, and a large series of urinalyses made by Slosse and his associates substantiates this. The favorable clinical experiences which have been recorded by a number of French writers in a measure may be explained by these findings.

An Effective Routine in Rheumatism. In view of the reasonableness of the attitude of the investigators whose work has just been quoted, there should be no doubt that the study of the thyroid aspect of rheumatism is well worth while. The use of my Thyroid Function Test in a number of cases has uncovered a real thyroid insufficiency, which previously had been overlooked, and with the information derived from this test in hand, there can be no guess-work about the application of thyroid therapy in the individual.

Since so many rheumatic individuals are not merely in a state of hypothyroidism, but in a general state of hypocrinism, i. e., there seems to be a general insufficiency of the ductless glandular activity as a whole, it is very proper to give some consideration to intimately associated glands as well as the thyroid, and this has been found to be very satisfactorily accomplished by applying concurrently with thyroid therapy the principle of adrenal support which has already been discussed quite fully. It will be found that many individuals with rheumatism are not merely subnormal from a chemical standpoint, but their circulation is poor, their blood pressure is very often much lower than normal, and too, they are very easily fatigued. In other words, they are suffering from a deficient burning up of the wastes of their own physiology, or chemasthenia, as I have termed it. To take care of this, as well as the thyroid side that has already been referred to, I have found considerable advantage from the use of *Adreno-Spermin Co.* (*Harrower*) which, as is known, is a combination of a small dose of thyroid with a suitable dose of adrenal substance and spermin from the interstitial cells of Leydig. The reasons for the first need not be mentioned again; the adrenal substance is given for its circulation-stimulating effect and for its influence upon the general tone of the body, whereas the spermin, in addition to being a synergist to adrenal

therapy, has a decided dynamogenic and musculotonic effect, which is always advisable in these cases. The *Adreno-Spermin Co.* is given in fairly generous dosage over a period of at least two months; longer if possible. Perhaps, at the beginning, one five-grain dose, three times a day, may be given for two weeks, after which one four times a day for another two weeks; thereafter two three times a day.

Acidosis in Rheumatism. Bearing in mind the tendency to acidosis so common in rheumatic patients, and the fact that the consensus of clinical opinion emphasizes the importance of alkalinization, not merely in rheumatism, but in all conditions of reduced cellular activity, the principle of remineralization, which is given full consideration in another chapter, certainly is an advantage in conjunction with the organotherapy just outlined. The use of the remineralizing formula, *Calcium Phosphorus Co.* (*Harrower*), in doses of three grams, powdered and taken with a generous drink of water, an hour before food, twice a day for a month and thereafter on alternate weeks, will supplement very materially the changes which we hope to make in the chemistry as a result of the recommended organotherapy, and in many instances the combination of these two formulas has made a remarkable difference in the rheumatism and its various manifestations.

Ovarian Form of Rheumatism. The ovarian form of rheumatism, if we may classify it as such, is another of the chronic phases of that malady and is often found in those who have a serious dysovarism, *especially in women at or following the menopause.* Clinically, this seems to emphasize the opinion that the ovarian principle has something to do with the maintenance of the body chemistry, and the removal of this factor, either by surgery, or by the usual change of life, favors the conditions which cause the rheumatism. This condition is likewise of endocrine origin, but instead of being due to thyroid insufficiencies, it is a result of ovarian insufficiency. It is quite possible, too, that its etiology is partly due to thyroid disturbances. At least it reacts more quickly to luteal therapy, especially if this procedure is applied early in the course of the disease. In this connection, Dalché's statement will be recalled, that the administration of ovarian substance has given very good results in instances similar to the above, and in suitable cases he occasionally combines thyroid and luteal substance.

I have had a number of very satisfactory experiences

from the combination of thyroid, for the reasons previously mentioned, and ovarian substance and corpus luteum, to take care of the ovarian aspects of the case. In other words, *Thyro-Ovarian Co.* (*Harrower*) has been given to women with a menopausal, rheumatic manifestation, with good results; and in some cases in individuals who have been treated previously for long periods without any permanent change in the rheumatism. The fundamental principle of taking care of all the various associated disturbances is another explanation for the advantage of this idea.

It is difficult definitely to state which case of rheumatism is of thyroid origin and which is not. According to Léopold Lévi and de Rothschild, the only way to answer this question is empirically to apply thyroid extract, and in explanation of this, they may be quoted as follows: "From the practical point of view, in all forms of rheumatism in which the cause is unknown, it is an advantage to apply thyroid therapy. In such cases there will be more chance of results if the subject is young, if the rheumatism is accompanied by subacute exacerbations, and if there is only slight deformity. In those cases where there is a decided thyroid influence the initial results will be rapid, sometimes immediate. If the treatment does not act immediately, it is advisable to vary the doses, sometimes reducing them and giving the remedy for a longer period. There is no doubt that this medication may render very great service in the treatment of certain rheumatics, without exposing them to the least danger." Of course Léopold Lévi looks at every disease from the standpoint of its relation to the thyroid gland—he has been called "thyroid mad"—but the fact remains that he and his associate, Baron Henri de Rothschild, are successfully treating scores of cases at their hospital with thyroid.

Thymus in Arthritis Deformans. The thymus is another gland which seems to be connected in some way with the joint manifestations of rheumatism, and several references have appeared in the literature in the last few years extolling the value of thymus extract in these chronic joint conditions.

Naturally, it is far from possible always to cure the disease, but according to Nathan, of New York City, the first and most important beneficial change due to the thymus medication is a reduction in the pain present, and later, provided the case responds to the treatment, there is an

increased mobility as well as general betterment of the nutrition and health.

It is not yet possible to explain why thymus medication does this and in what mysterious manner these results are brought about, but we know, at least, that in early life the thymus controls in a considerable degree the mineral metabolism, for it will be recalled that thymectomy causes a remarkable softening of the bones and an obvious disturbance of mineral metabolism. It may be therefore, that there is a principle in thymus extract which favors the reëstablishment of the disordered metabolism of calcium salts, which is undoubtedly a factor in these rheumatic cases, and that the benefit is due solely to this. Suffice it to say that in the treatment of arthritis deformans Nathan recommends 15 or more grains of thymus substance three times a day given for weeks or months and that some very encouraging results have been reported.

A Pluriglandular Formula. Early in the work of this laboratory I was importuned to make a combination of *Adreno-Spermin Co.*, previously mentioned, and thymus substance, which had been done some years before by Nathan. For some time a preparation known as *Thymus-Spermin Co.* (*Harrower*)—No. 57 on our list—was prepared as a special formula for the few physicians who chose to use it. I was never very enthusiastic about it. In February, 1920, I published in *The Organotherapeutic Review*, a brief item from a more recent paper by Nathan ("An Experimental and Clinical Study of Arthritis Deformans as an Infectious Disease," *Jour. Medical Research*, May, 1917), in which appeared the following sentence: "I can only say a few words as regards the treatment of this condition. Some years ago I strongly advocated the use of thymus extract in the treatment of these diseases. At that time I stated that this substance is not a specific, and, from what has been said in the foregoing pages, there can, of course, be no doubt in regard to this. The fact nevertheless remains that thymus seems to have a very definite beneficial effect upon the nutrition, and I still find that in those cases in which the joints are not destroyed or ankylosed (provided it is long continued and the routine dieting and mechanical treatment which are so harmful are omitted) *it nearly always leads to more or less complete recovery.*"

In my comments upon this quotation I said, "This method of treatment fails very often, I am sorry to say. For two

reasons: (1) Arthritis deformans usually involves too great an organic or structural change in the bones and joints, and (2) also because the treatment is not given with sufficient persistence." Another factor worthy of mention in this connection concerns the generally reduced oxidation and elimination in these cases; and here my pluriglandular formula *Adreno-Spermin Co.*, theoretically, should be of considerable value. For the convenience of several friends I have combined equal parts of this formula with an active preparation of thymus gland, and this should be given in amount of four to eight 6-grain doses a day for some time as an adjuvant to other accepted treatment in chronic arthritis deformans.

I have had a number of encouraging reports and presume that there are just as many discouraging ones which have not come to me.

I remember at a lecture in Chicago that I had been asked for my opinion of the possibilities of organotherapy in chronic rheumatism and arthritis deformans and gave a very noncommittal reply. A gentleman got up and asked for the privilege of making some remarks and said that at that very moment he had on his list no less than seven persons with varying degrees of rheumatism, ranging from a chronic rheumatism to a serious rheumatoid arthritis, all of whom had been given *Thymus-Spermin Co.* (*Harrower*) in periods ranging from a month to six months, and all of whom had been very decidedly benefited by the treatment. A number of other reports, both verbal and by letter, have confirmed this impression, but I cannot but have some qualms in urging the use of this formula merely because in too many of the cases conditions have advanced to a point where no results can be expected. If the physician and the patient are convinced that there is practically no hope from other therapy, and they feel justified in giving this a trial, they will have done exactly as a good many others have done, and in a proportion of the cases, even though it may not be so very large, some encouragement may be expected.

In conclusion, let us remember the intimate relation of the ductless glands to metabolism, the undoubted connection between rheumatism and metabolic disturbances and, therefore, the possibilities of organotherapy as a meritorious adjunct in the treatment of certain forms of rheumatism.

SECTION V. CHAPTER 19

THE ENDOCRINES IN DERMATOLOGY

The principal manifestation of disturbance of the chief endocrine gland—the thyroid—is a change in the skin. Myxedema, as its name implies, is referable to a dermatosis, even though its influence upon the body extends very much deeper. In a paper entitled "The Ductless Glands and Dermatology," Cunningham of New York (*N. Y. Med. Jour.*, Jan. 19, 1918) has well said: "The internal secretions dominate the vital functions. Distressing, disabling, and even fatal consequences follow, in the general economy, interference with their normal operation. Is it a far cry from this to the inclusion within the scope of their perverted activities of the many mysterious maladies that assail the skin? The greater includes the less. The envelope of the body cannot escape the deterioration of the whole."

The thyroid evidently exerts a definite influence upon the nutrition of the skin, for hypothyroidism has among its symptoms many disturbances of the skin and its appendages. In addition to a direct relationship between the function of the thyroid and the skin, there is an equally important indirect relationship. For example, it is well known that the thyroid presides over the metabolism of the body and is an important part of the detoxicating mechanism. If, then, there is a deficiency in the function of the thyroid, naturally there will be a change in the body's powers of burning up wastes, and since a part of the duty of the skin is to facilitate the elimination of certain wastes it is not unreasonable to connect certain dermatoses with the deranged chemistry of thyroid origin!

It seems that the first effort to apply thyroid therapy in serious dermatoses was that of Byrom Bramwell, of Edinburgh, who in 1893 recommended the advantages of thyroid feeding in psoriasis, scleroderma, and other systemic skin disturbances. Much of the good that was reported so long ago was discounted, and, as MacCleod has it, (*Practitioner*, Feb., 1915, p. 298) "its further use led to frequent disappointments and, like the proverbial rocket stick, it came down from being regarded as a panacea for all manner of scaly dermatoses to being almost entirely neglected."

This is exactly what has happened to other phases of

organotherapy, and, as I have repeatedly shown, much of this reaction was due to ignorance and especially to a failure to consider the relations of these glands.

The Thyroid Manifestations. In a fairly extensive literature there is found evidence that the discovery of hypothyroidism, and its treatment with suitable thyroid therapy, has changed the character of the skin as by a miracle. Previously it had been rough, scaly, and cold to the touch, with falling hair, cracking nails and a marked degree of "skin inactivity." And not merely was the appearance of the skin changed but so were its circulation and functional usefulness. It is quite interesting to contrast the dry, rough, harsh, cold, inactive skin of hypothyroidism with the moist, thin, easily flushed and hyperactive skin of hyperthyroidism.

Among nutritional or systemic dermatoses associated with the infiltration of hypothyroidism (see especially Section IV, Chapter 3) are psoriasis—already mentioned as having been among the first dermatoses to be treated with organotherapy—ichthyosis, xeroderma, scleroderma, pityriasis, and certain forms of eczema.

Psoriasis. I have seen considerable benefit follow the use of suitable organotherapy in psoriasis despite the unresponsiveness of this particular dermatosis to any form of therapy. I confess that my attitude to the use of glandular remedies always has been to consider them as adjunct measures, and whenever I have been asked for my opinion of the value of a remedy I have urged its use in conjunction with suitable eliminative, dietetic and medicinal measures. Some of my well-meaning friends have immediately said that the good from the treatment might as well have been due to the associate treatment as to the organotherapy —and I admit it very frankly—but it is perhaps, more than a coincidence that some of these patients had been taking their treatment for 10, 15 or 20 years with not more than a passing benefit, and now, by the transforming influence of endocrine therapy, plus needed associate treatment, were decisively benefited or even cured.

The most valuable organotherapeutic remedy in psoriasis is thyroid extract, and the dose ranges from 1-8th to ½ grain three times a day. Where the patient also has a syndrome of hypoadrenia—and this is very common and easily determined by finding a marked asthenia, low blood-pressure, deficient circulation, poor elimination, etc.—

Adreno-Spermin Co. (*Harrower*), combines with thyroid treatment a suitable and needed adrenal support of the increased circulation and ensures better cellular chemistry. This favors just the change needed to reflect itself upon the disordered skin functions. In psoriasis this treatment, coupled with purin-free diet, thorough elimination, and chrysarobin, is a considerably better routine than to depend upon the chrysarobin alone, as has been the manner of some.

The one thing regarding the etiology of psoriasis that is supported by the most substantial therapeutic results concerns its metabolic origin. Many times it has been found that the ingestion of certain animal nitrogen products precipitates the attack or prevents its recession. A diet regulated upon this hypothesis frequently appears to modify the progress of the disfiguring eruption. As we have seen, the thyroid has a marked influence upon the nitrogenous metabolism, and, according to Cunningham, "its applicability therefore to the treatment of psoriasis would seem to be perfectly logical, and it is to the thyroid that the empiricist-experimental clinician should turn for the most promising lead in this etiologic hunt."

Léopold Lévi and his associate, Baron Henri de Rothschild, report several cases of psoriasis which were associated with chronic rheumatism and in which the psoriasis completely disappeared under thyroid treatment. (The subject of the important endocrine aspects of rheumatism, as discussed by these writers and others, is given further consideration in Chapter 18, of this section.)

Finally, Sir Malcolm Morris, the famous British dermatologist, speaking of the importance of the thyroid aspect of psoriasis, (*Brit. Med. Jour.*, May 17, 1913), remarks that he "has found thyroid therapy especially efficacious in those cases of psoriasis which were associated with adiposity"; in other words, evidently the more definitely thyroid cases. He adds: "In no skin affection has thyroid medication given better results than in psoriasis," and he emphasizes the fact that "whenever cutaneous affections are found associated with other conditions in which thyroid is indicated, there is a presumption in favor of thyroid treatment."

Scleroderma and Ichthyosis: The superficial resemblances of these conditions to the roughened and thickened skin of myxedema has prompted many to attempt thyroid therapy, and, in a proportion of cases, the results have been quite

encouraging, more especially when these dermatoses are found in children and infants. In passing, it is particularly worth while to consider organotherapy for dermatoses in children who manifest other evidences of endocrine imbalance,and it is equally true that quite a number of developmentally defective children known to be suffering from dyscrinism have, in addition, various more or less intractable dermatoses, especially the two under consideration for the moment. Morris reports that he has used thyroid in a number of cases of ichthyosis "and in none without benefit." It is interesting to note, in passing, that this writer does not hesitate to say that he "has been especially struck by the influence of thyroid in alleviating pain which is not infrequently a symptom of keloid."

My advice in regard to the treatment of xeroderma, scleroderma and other similar skin affections, where thyroid is called for, is to use *Thyroid Co.* (*Harrower*) gr. ½, a combination of an official tested thyroid product with the alkaline, remineralizing salts (representing those found in the blood)—in the following step-ladder fashion: For ten days or two weeks, or even longer, give one dose a day at any convenient time. For a similar period, ten days or more, give two doses a day. For a third similar period give three doses a day, one at each meal, and, if it seems advisable, for a fourth period give four doses a day. During these periods of gland feeding the patient should be watched, and the response to the organotherapy in various ways noted carefully. This may be followed by a rest of the same length, or twice as long as each 10 or 15-day period, and then the whole thing can be repeated. In many instances benefit will be seen within two or three months; and I was both amused and pleased just the other day to hear a prominent sanitarium superintendent remark over the telephone to the effect that Mrs. Blank "could wrinkle her face again"—she had been taking for about 3 months, a treatment which I had recommended for scleroderma.

Eczema. Too often, eczema is an infection of the skin that has been made possible by a particularly lowered resistance—many times of endocrine origin—for the capacity of the skin to function normally and to resist infections is related to a normal endocrine service to the body. Eczema is commonly found in "run-down individuals," and my personal opinion is that, the nutritive and circulatory influence of the thyroid and allied glands upon the skin having been lessened, lurking infections have a chance to

take hold and the difficulty assumes a double aspect—infective as well as nutritional. Occasionally, a treatment directed at the infective aspects of eczema is eminently satisfactory, but, as I see it, the advantage in many instances is as much due to the associated general treatment, which gives the regulating endocrines a better chance to reassert themselves, as is always the case when the emunctories are encouraged and elimination is better. In some cases of eczema, on the other hand, "all sorts of treatment" fail miserably. I recall the incident of a little child with a terrible eczema of the scalp which was perfectly horrible to look at. It had been dusted and dabbed and daubed for many months and appeared to be worse than ever and a source of great discomfort to the mother as it must have been to the child. It was cured as by a miracle with a few weeks of thyroid therapy, and incidentally served as a means to the physician's conversion to the possibilities of organotherapy, in the routine use of which he is now an enthusiast.

Still another youngster of three of four years had eczema of the scalp, which had been a source of great concern to the physician father. This child was said to have never had a complete night's sleep in her life. When she did get to sleep the most unusual precautions were taken to prevent her from awakening, because it was known that another hour or two would be spent in getting her to sleep again. I went out to see her, mentioned to the parents the probability of the thyroid origin, advised suitable thyroid therapy and alkalies as previously mentioned, *and she was well in six weeks*, much to the amazement of all her relatives, for her condition had lasted from infancy.

Eczema in children apparently has a larger thyroid phase than eczema in adults, and the results are comparatively better the younger the case. In adults, on the other hand, some eczemas apparently are not likely to respond to thyroid or any other endocrine therapy; but since one cannot determine this in advance, it seems not unreasonable—even though quite unscientific—to give these patients the benefit of organotherapeutic treatment, which possibly is no more scientific than recourse to any other unsatisfactory and useless measure, and most of the patients will admit that they have tried many measures for a number of years with considerable misgivings, but usually are perfectly willing to have another "shot" which frequently hits the mark.

Acne. Acne and other inflammatory conditions of the sebaceous and sweat glands apparently also may be related to dysthyroidism in the same manner and for the same reasons discussed under subject headings. It happens, however, that in many instances acne also is related to a change in the function of the sex glands, which may account for the frequency with which acne is found at puberty in boys and in relation to menstrual difficulties in girls. Local treatment of the acne is quite necessary, the expression of the comedones, and the use of suitable lotions, are perfectly in order, as to my way of thinking, is suitable vaccine therapy; but in all of these cases there is good reason to consider a prospective endocrine basis, and, if it seems advisable, to treat it along with the rest of the patient. Quite a number of cases of acne in girls have been cured entirely by the regulation of an associated dysovarism by means of *Thyro-Ovarian Co.* (*Harrower*), so much so that some physicians have come to consider this pluriglandular formula as a remedy for acne when, in point of fact, it is not.

Dermatoses of Ovarian Origin. The relation of dysovarism to skin diseases has been discovered by many clinicians. We have already noted the frequency with which acne may be related to menstrual difficulties in girls, and, among a number of writers, Bandler believes that the dermatoses of pregnancy, menstrual disturbances and the climacterium "are of the same kind and nature as those occurring with anomalies of menstruation and are dependent on altered endocrine secretions."

Many times an intractable dermatosis has been modified or even cured in conjunction with the needed regulation of a complex based upon dysovarism. Especially is this true at the menopause. Graves, of Boston, reports favorable experiences with ovarian therapy in women whose dyscrinism was accompanied by such skin troubles as pruritus vulvae and severe furunculosis of the external genitalia of years standing. Several other writers have added to the consensus of opinion that certain skin diseases occurring during the menopause, as eczema, prurigo, and psoriasis, disappear following the organotherapeutic regulation that is demanded in such cases.

Circulatory Skin Conditions. In addition to the disturbances already mentioned, several other derangements of the skin must be considered as having a clear-cut endocrine origin. Scholtz, a leading dermatologist in Los Angeles, in his paper "The Skin as an Index to Health" (*Med. Rec-*

ord, May 15, 1920) notes that "The frequent observance of disorders of internal secretions in a very large clinical group of angioneurotic dermatoses . . . . is highly suggestive of the close association and correlation of the sympathetic vasomotor nervous apparatus and the ductless glands." Raynaud's disease, and even the localized gangrene, found in advanced cases, have been connected with the thyroid and cured time and time again. Even chilblains are considered as definite in this category. According to Cunningham (*N. Y. Med. Jour.,* Jan. 19, 1918), "erythema pernio (or chilblains) is so clearly a circulatory derangement that involvement of the adrenals is certain. This may be due to toxemia, to which, as we have seen, the adrenals are particularly liable; it may be due to thyroid insufficiency reacting upon the adrenal glands." Here again, the metabolism-stimulating, circulation-regulating pluriglandular formula, *Adreno-Spermin Co.* (*Harrower*), has been used with or without additional therapy in circulatory stasis and localized disturbances. Since the endocrine glands, and especially the thyroid and adrenals, have so much to do with vasomotor control, it does not seem so unreasonable to consider disturbances of the type under discussion as in the nature of local syncope, associated, perhaps, with a local asphyxia, as Cunningham calls it.

Pigmentary Skin Conditions. Since the pigmentation of the skin is believed to be modified by internal secretory functioning, some effort has been made to translate this to therapeutic advantage. It is well known that serious adrenal diseases are connected with a pigmentation of greater or less degree, and, in certain instances, that adrenal therapy (the administration of adrenal substance by mouth) has been followed by a reduction in the size and color of the pigmented areas. Bandler and others suggest that the pigmentary signs of pregnancy also indicate that the gonad function may be concerned in the normal pigmentation on the skin and that there may be a gonad aspect to certain pigmentary difficulties. It is well known also that one of the signs of myxedema is yellowish coloration of the skin, and certain French investigators report that abnormal conditions of pigmentation are beneficially affected by thyroid treatment, even indicating that leukoderma may be treated with advantage by thyroid or adrenal therapy.

Of course, so-called "liver spots" or chloasma, and the pigmentary condition of the face described by some as "alimentary pigmentation," usually beginning near the eye-

lids and spreading gradually over the face, have to do with the detoxicating organs, chiefly the liver and the thyroid and many times are remedied by a generous stimulation not merely of the digestive organs—as, for example, with *Secretin Co.* (*Harrower*) (see Section V, Chapter 24)—but also by step-ladder dosage of thyroid, as mentioned previously. All of this emphasizes our need for study of the changes that the thyroid may undergo in cases of intestinal toxemia, and the importance of regulating the endocrine aspects of this most common occurrence.

The Hair and Nails. Closely related to the disorders of the skin are disorders of its appendages. The growth of hair is certainly in some way connected with the endocrines, and, by some, baldness is said to be due to hypocrinism, and, on the other hand, hypertrichosis to an excess of certain endocrine activities, especially of the adrenal cortex, and perhaps a part of the pituitary gland. Léopold Lévi reports examples of the advantages of thyroid therapy upon the growth and color of the hair, and according to Morris: "There is reason to believe that the pituitary and the adrenals take part in the trichogenic function, and it has long been known that the growth of hair is caused directly or indirectly by the sexual glands. Some incline to the view that the thyroid chiefly influences the hair and scalp while the sexual glands affect the pubic and axillary hair, and the beard."

Urticaria and Herpes. Attention already has been called to the responses occasionally found in the skin to protein sensitization, or anaphylaxis (see Section II, Chapter 7). Apparently the skin is the victim of circumstances, and since these circumstances involve the endocrines in a way that is not quite clear, but which has been discussed previously, when one is confronted by a condition akin to urticaria, no harm can come from extending one's knowledge regarding the endocrine aspects of the case, whether prominent or apparently covered. Tremendously uncomfortable wheals of urticaria have been dissipated in 10 minutes by hypodermic injections of adrenalin chloride, 5 to 8 minims of a 1:1000 solution. Urticaria, and especially herpes zoster, aggravated at or near the menstrual periods or of menopausal origin, has been entirely cured by organotherapy directed at the ovarian imbalance—*Thyro-Ovarian Co.* (*Harrower*).

Angioneurotic Edema. This is another of those peculiar dermatoses believed to be related to endocrine dysfunction

A most interesting consideration of this subject appeared in a paper by Green, of Los Angeles, which was submitted in the first Harrower Prize Contest and is published in "Essays on the Internal Secretions—1920," page 273. According to this writer, who substantiates his opinion with a number of quotations from other authors, angioneurotic edema is believed to be a pluriglandular hypersecretory syndrome in which thyroid excess is a preliminary feature and adrenal hyperactivity the secondary and predominating characteristic. The treatment recommended should be that for mild hyperthyroidism. Among the organotherapeutic remedies for this condition is pancreas substance.

Conclusions. In concluding this brief consideration of organotherapy in dermatology, it should be clear that the endocrine glands are concerned intimately in those functions of the body which may come to concern the skin, and, further, that the nutrition and circulation of the skin itself are very closely under the control of those glands. Many dermatoses are of pure thyroid origin. The circulatory-nutritive-metabolic imbalance of the thyroid and the adrenals, which is encouraged by pluriglandular therapy—formula *Adreno-Spermin Co. (Harrower)*—is often related tc the cause of certain dermatoses and, when regulated, helps to dispose of them.

Gonad dysfunction, too, has its part to play, not merely in the direct manner suggested, but probably also because of the intimacy between the thyroid and the sex glands.

Finally, as Cunningham says: "In endocrinology will be found the touchstone of dermatology," and success in the treatment of dermatologic disturbances is more likely to be ensured if endocrinologic derangements previously overlooked are brought into prominence and then properly disposed of.

SECTION V. CHAPTER 20

ORGANOTHERAPY IN PROSTATIC DISORDERS

The prostate gland is one of the least understood glands of the body, at least insofar as any possible internal secretory function that it may have is concerned, and in regard to its relation to the other endocrine organs and especially the gonads. Information regarding the experimental effects

of prostate extracts and of the use of prostate preparations in clinical practice indicates that there are certain therapeutic possibilities, but the subject is by no means well understood, and this statement necessarily must be incomplete and in some measure indecisive.

Certain clinical disturbances of the prostate undoubtedly are associated with the sex manifestations, and it is fair to presume that the prostate is involved in the reproductive function in a considerably broader manner than its production of the seminal plasma.

Prostate Hypertrophy as a Compensatory Manifestation. The fact that prostatic hypertrophy quite commonly follows the functional retirement of the testes would indicate that there might be some relationship between the endocrine activities of both these glands. It has been suggested that there may even be a friendly hyperactivity of the prostate; that is, when the testes become functionally inactive, the prostate may be enlarged in a compensatory fashion, just as we know various other ductless glands may enlarge when other closely related endocrine organs are put out of commission. At least, we know that, provided we can exclude deep-seated and overlooked infective processes and essential new growths of the gland such as adenoma or cancer, there evidently is a form of enlargement of the prostate connected with waning gonad function which, theoretically, ought to respond to an organotherapy which would supplement the endocrine function of the testes and thereby lessen the probable necessity for overactivity on the part of the prostate. The idea of a compensatory prostatic hypertrophy is not yet a proposition accepted by urologists, but the treatment of it, based upon the outlined idea, has been most encouraging. In conjunction with several prominent genito-urinary specialists, a special formula has been developed in my laboratory, called *Leydig-Cell Co.* (*Harrower*) (No. 41), the essential basis of which is an extract of the interstitial cells of Leydig, undoubtedly a useful organotherapeutic remedy since these cells are the essential structure of the sex glands, which some even suggest properly might correspond to a "male corpus luteum."

Hypoprostatism and Neurasthenia. A number of reports in the literature, as usual especially in French, state that there is a therapeutic value inherent in desiccated prostate substance, that it meets the expectations of a homostimulant gland extract and is therefore likely to be valuable in conditions of prostatic insufficiency. It has been re-

commended chiefly as a remedy in the neurasthenic manifestations accompanying prostatic disease and following prostatectomy, and as an advantageous addition to the Brown-Séquard method of treatment for presenility, impotence and certain functional sex neuroses. Laignel-Lavastine, a famous Parisian neurologist, tells of good results from this procedure, and Beard, Blanche and others agree with him.

To meet a demand for a preparation of this character, No. 48, *Prostate Co.* (*Harrower*) has been prepared, each six grains of which contains 1½ grains each of the desiccated prostate substance, interstitial cells of Leydig (spermin extract) and lymphatic gland substance, together with an effective dose of nucleinic acid. The latter is added because of its leucocyto-stimulant effect and its well known value in conditions of lowered resistance where infections are or have been involved.

A personal experience with this was quite encouraging: The patient, an old soldier-chaplain, age 81, was sent to me in the hope that something might be done to relieve him, for after long periods of treatment for prostatic and urinary difficulties he was in a deplorable state. I am not a genito-urinary man, and hesitated to have anything to do with such a case. He had a very much enlarged prostate, much urinary difficulty and a most obstinate form of constipation. He was very old and frail, with a bad heart and no leaning to surgery. I therefore advised the *Prostate Co.* on what I called "half a chance." Here is a report which he made some months later: "I am much better. There seems to be more 'pep' to the contractile force of the bowel and less obstruction to the passage of feces. A noteworthy point is that the diameter of the stool is much larger during each course of the capsules. The difficulty with urination is almost gone, and with two or three short exceptions I have had none of the troubles of this nature (dysuria and frequent micturition)." In this case, there was a decided reduction in prostatic size and tenderness; the results were doubly remarkable because of the age and condition of the patient. Many reports convince me that functional prostatic disorders have been benefited by the use of this formula.

A Prostatic Form of Impotence. Another practical application of prostatic organotherapy was first suggested by Bazy. He found it valuable in "prostatic impotence"—that form of sex debility in which prostatic hypertrophy and

hyperesthesia was or had been prominent. Usually these cases have suffered from emissions, premature ejaculation and the usual host of neuropsychoses of the "sexual neurasthenic." In developing these notions, Reinert found that such chronic prostatic enlargements were reduced and that simultaneously urinary retention and tenesmus were diminished, while in younger cases there was occasionally excellent control of the hyperesthesia and its associated disturbances.

Still another preparation of this character has been the subject of considerable recent study and clinical application. Under the name *Gonad Co.* (*Harrower*), a combination similar to the last but containing in addition an extract of the anterior lobe of the pituitary gland, has been made and used chiefly for the attempted reëstablishment of lost sexual powers, with an aggregate of results which have made a number of those using it remark that "it is the most effective thing that I have ever used or recommended." This particular phase of organotherapy, which is a considerable advance over the original Séquardian measure, is more thoroughly discussed in the following chapter, "The Hormones in Impotence."

Limitations of Organotherapy. In closing, it should be remembered that glandular extracts of the character under consideration exert a specific influence upon the glands to which they correspond and must not be expected to develop results beyond their scope. The endocrine function of the testes is not, by any means, its spermatogenic function, though doubtless the two are related, and the reëstablishment of the gonad endocrine function does not necessarily involve the restoration of fecundity. It seems, however, that the ductless glands involved in the generative process, aside from the gonads or essential sex glands, exert a paramount influence upon the effectiveness of these organs; and it has been shown many times that aspermia, as well as Leydig cell incompetence, has been reëstablished by thyroid or pituitary medication, hence the inclusion of preparations of this character in a remedy from which one expects tonic qualities is in order, the more especially when the importance of the anterior lobe of the pituitary is remembered in connection with gonad development, as emphasized by Froehlich, Bartels, Cushing and many others.

Prostatic troubles, *when functional,* properly may include organotherapy, for the results may not be merely of prospective help to the patient, but of diagnostic value also.

SECTION V. CHAPTER 21

THE HORMONES IN IMPOTENCE

The subject under consideration still may be considered by some to be "delicate" and, perhaps, even improper, for, unfortunately, traces of the old-fashioned prudery, which has left its mark upon the civilized peoples of this world, still remain.

Gonad Dysfunction. However, the reproductive organs, and especially the sex glands, or gonads, like other glands of internal secretion, are subject to disorder or structural disease, and since these are among the really important glands of internal secretion, either we must ignore the subject as some may do, or we must consider it as probably worthy of careful study and comment. Many seriously important factors depend upon proper gonad functioning, and, fortunately, in many instances these are amenable to indicated organotherapy. It is proposed to call attention especially to the possibilities of pluriglandular therapy in modifying the results of what properly may be called *hypogonadism*, that is, reproductive or sexual insufficiency.

On May 16th, 1888, the renowned Brown-Séquard demonstrated in his laboratory in Paris, on himself as the subject, the remarkable results following the use of a pinkish liquid obtained from the testes of a dog. His reports, the first of which was made to the Paris Academy of Medicine and published in his own *Archives de Physiologie,* (1889 vol. xxvi, p. 651; also p. 739), were really the beginning of scientific testicular organotherapy, although there are references to the cruder and empirical application of this idea in the uncanonical books of the Bible and the writings of physicians and philosophers thousands of years ago.

Unfortunately, the charlatans of Paris promptly seized upon Brown-Séquard's announcement, seeing therein a chance to dupe their susceptible cases of still more money, and the subject shortly fell into disrepute owing to the fact that the noise of the charlatans squelched the real scientific statements of this famous physiologist and his associates. To this day this "black eye" has remained, and many physicians subconsciously feel that testicular opotherapy "savors of quackery."

The fact remains that the fundamental principle of organotherapy which was proved by Brown-Séquard in his

own body and has since been duplicated times innumerable by reputable physicians, is as rational and physiologically sound as any other method of glandular therapy. It has always seemed strange to me how willing some physicians are to use ovarian therapy when indicated and how reticent they are about the use of "orchic substance."

The Dynamogenic Effect of Spermin. Briefly, this form of treatment offers two important therapeutic possibilities: (1) It increases *dynamos*—muscular, nervous and sexual; and (2) it homostimulates the gonads just as other endocrine extracts homostimulate the organs corresponding to those from which they were made. It is interesting to recall that Brown-Séquard found a marked increase in his mental and physical vigor—he was a man in the seventies—and in his own words, "Considerable laboratory work hardly produced any fatigue, and to the astonishment of my two principal assistants and other persons I was able to carry out experiments for several hours in a standing position, with no desire to be seated." The dynamometer has been used to establish this fact accurately, and Mosso's ergograph has shown definite dynamic increases following this organotherapeutic procedure.

Despite many adverse critisisms there is quite a large literature on the subject, including the well-known book by Prof. von Poehl, of Petrograd, who a number of years later isolated from testicular extract a crystalline principle which he designated "sperminum." It is thought to be the essential stimulating principle in this extract, and abundant literature exists upon its pharmacodynamic influence. Gonadotherapy accordingly has established itself as one of the really important branches of hormone therapy.

The disparaging criticisms referred to have been largely based, to my way of thinking, upon the foundation to which I have elsewhere made reference, as well as upon the failures which inevitably must follow the use of such a measure when the fundamental causes are ignored and the treatment continued only for a limited time. The fact remains that two thirds of the unkind things said about organotherapy have been based on half-way work and the setting of one's hopes too high and testicular organotherapy is one form of gland feeding upon which great expectations are placed, while being in many cases but little deserved.

Quite an interest was aroused at the time by the publication of my review of the sixth edition of Dr. V. G. Vecki's splendid work on "Sexual Impotence." He is a pioneer in

the field which he has chosen, and his book is worthy of all the encomiums that I can write about it. For years we groped around, but now endocrinological studies have established many facts, determining the importance of the endocrines in gonad dysfunction, and, as Vecki enumerates them, it is clear that these facts establish the importance of the relations of these glands. For instance, he brings proof to connect the pituitary gland, especially the anterior lobe, with gonad development and function. The adrenals are also concerned, especially the cortex. "It is positively established 'that the thyroid cells form an internal secretion, which acts as a chemical stimulus to other tissues,' though Howell cautiously states that this is 'usually assumed.'" The importance of the thymus in sex development is not overlooked, and I was glad to see that Vecki has found a persistent thymus as playing a part in the syndrome of hypogonadism, just as I have many times, and in both sexes.

Impotence in the Male. Much interest and speculation in regard to functional agonadism developed as a result of the unwarranted newspaper notoriety early in 1920. I was compelled to work overtime answering questions about the now-famous "interstitial glands." Too much has been published on the subject and the hopes of too many have been aroused unfairly.

I want to emphasize a few points about agonadism with its resultant impotence. First of all, organotherapy is effective in proportion to the reactivity of the organism to the hormone stimuli that may be represented by the glandular medication that is given. This means that the individual factor, the responsiveness of the organs to homostimulation, is paramount. If the testes are atrophied or senile, neither transplantation nor organotherapy can be of the least service. If there is a structural change in the glands, as, for instance, that due to tuberculosis or a tumor, it is not likely that this measure will be beneficial.

Again, if infective causes, especially in the prostate, epididymis and adnexa, are allowed to remain hidden and untreated, it is foolish to depend upon any treatment, no matter how prospectively efficacious, until the underlying conditions are discovered and remedied. Another very important factor concerns the psychic element. Obviously, uncontrolled influences, which are active through the effects that they exert through mental channels, must be ruled out or overcome before a functional impotence can be helped.

Of course, there are many cases of asexualism that are purely functional. Cases have repeatedly come to my attention when a severe fright, an accident, or a near accident (where a serious danger was narrowly averted) have been definite causative factors. Post-influenzal impotence is quite common. In fact, the same etiological factors may cause functional agonadism with a resultant impotence as will deplete the adrenals. These are overactivity, overstimulation by toxemia, especially from a focus of infection, and emotional causes such as fear, etc.

Perhaps one half of the usual grist of cases are purely endocrine, and hence likely to respond to suitable organotherapy; but this is not saying that the other half are sure to be benefited, for they are not. Sometimes the organotherapeutic régime may be the chief means of differentiating between the functional and responsive form of impotence and the less easily modified structural cases.

Another important point: So often functional impotence is not solely a disturbance of the interstitial cells of Leydig alone; and hundreds of clinical tests have shown that to combine with spermin (the essential active element of the interstitial cells) the synergists from the anterior lobe of the pituitary gland, the thyroid and the prostate, makes a much more likely-to-be-effective remedy.

Not long after the establishment of The Harrower Laboratory, several years ago, I was invited to collaborate in the experimental development of several pluriglandular formulas for the treatment of impotence and asexualism. Several interested genito-urinary specialists permitted us to coöperate with them, and eventually a pluriglandular formula was developed which since has been used with success in many hundreds of cases. This formula, the seventieth experimental preparation made in our Glendale laboratory, is called *Gonad Co.* (*Harrower*) and is a combination of several products of closely interacting endocrine glands. Let it be said here, in no uncertain terms, that we have not discovered a "cure for lost manhood." Full well do we know that this will never emanate from any laboratory, for the personal factor far transcends the physiologic. Nor do we believe that it will replace worn-out organs or reduce the age of those who may be induced to take it. We do feel, however, judging from the encouraging letters and appreciative comments which come to our desk from month to month, that something really worth while is being accomplished..

A Brooklyn, N. Y., urologist, who helped to originate the formula just referred to, and who has given the subject much study and practical investigation, argues—and I most thoroughly agree with him—that the preparation of the essential endocrine cells of the testes (the interstitial cells of Leydig, as they are called) does homostimulate the corresponding cells in those to whom it is given. In such cases, the addition of other synergistic gland extracts should be helpful, for the same reason that combinations of various endocrine products excel single extracts which may be indicated in other disorders. Among the most obviously helpful of these synergists are the anterior pituitary gland, the thyroid, the prostate, and the lymphatic glands, for reasons which will be entered into below.

The reason for making this formula so comprehensive is that experimental-clinical experiences established it to be more effective than others of a more limited character, and to satisfy those who feel that this may be a "shotgun" preparation the following fairly reasonable explanation is made:

In impotence there is usually a large neurasthenic element, for obvious reasons, and in addition to an asthenia of gonad function there is certainly a "run-down" condition which is identical in character with the adrenal insufficiency which has been discussed fully in other articles. In other words, the majority of these cases require adrenal support and should have it. Hence *adrenal substance* is one of the ingredients of this formula.

There is another important reason, which is found in the fact that the adrenal cortex (adrenal substance contains about 85 per cent. of adrenal cortex as compared with 15 per cent. of the medulla) is recognized as playing an important part in the development of the gonads, and a dozen or more references in the literature indicate that the corticular principle is an activator not merely of sex-gland development but of its function as well. (Parenthetically, it may be remarked that the condition known as "hypernephroma," in which there is an enormous hypertrophy of the adrenal cortex, usually is made manifest by a degree of sexual development and precocity which is quite out of the ordinary).

Other Endocrines Which Cooperate With the Gonads. For very similar reasons *thyroid extract* is a part of the formula. First of all the "condiment value" of small doses of thyroid in pluriglandular formulas must be mentioned.

Hundreds of tests have proved that this empirical use of thyroid does "bring out the flavor" just as a condiment, and adds to the efficacy of the formula. Further, in asthenia, hypothyroidism—even though it may be of a minor type—is an important possibility. There is also plenty of evidence to indicate that the thyroid gland, too, is a responsible factor in initiating and maintaining normal gonad activity, whether in the male or female—else why should the cretin, with its athyroidea, have no noticeable sexual development? Further, in conditions of cell laziness and senility, as well as in conditions where the gonads are below par, so also is the thyroid. This is both a causative and a resultant factor; and I believe that a small dose of thyroid is an eminently suitable remedy for the hypothyroid manifestations of the asexual as well as in the elderly individuals whose hormonic functions are on the wane.

We now come to one of the really important phases of this subject. The *pituitary body,* especially the anterior—or glandular—portion, is fully as important a factor in the development and maintenance of gonad function as any other endocrine element. This has been proved and reproved from several standpoints. For instance, hypopituitarism—or the Froehlich syndrome—frequently known as *dystrophia adiposo-genitalis,* always includes a disturbance of gonad function. This aspect of these cases probably is as important as any other, for infantilism—lack of the development of the essential sex characteristics—may be purely of pituitary origin. Again, an acquired pituitary dystrophy may nullify the physiological efficacy of the already established gonad function and not merely destroy the hormone-producing capacity of the sex glands, but actually cause an atrophy of all the reproductive organs in both sexes; and, still more remarkable, it usually causes a retrogressive change in remotely situated locations that are known to be related to those developments of feature and form that are connected with puberty—that period of initiation of gonad endocrine activity.

Now, in hypopituitarism, pituitary therapy may modify not merely the pituitary aspects of the case, but the gonads themselves also, and this method of treatment is recommended for both these purposes. Why not, then, consider the possibility of a pituitary aspect of asexualism, even though the patient may not have well-defined dyspituitarism? As a matter of fact, there are a number of references in the literature to the efficacy of *anterior pituitary sub-*

stance as a sex stimulant, and reports in the literature indicate that impotence in both sexes has been benefited by this method alone.

It has seemed that the *prostate gland* is involved in many cases of functional impotence and that prostatic therapy has been beneficial, especially in those forms of impotence that are related to a demonstrable disturbance in prostatic form and activity. The prostate is, indeed, a gland which has some broader physiologic influence than the production of its seminal secretion. Many writers believe that it is a real endocrine organ; and experience shows that to add prostatic extract to the other gonadostimulant extracts (as, for instance, those just mentioned) is worth while. Hence, this substance has likewise been added to the formula.

Finally, and most important, the gonad principle known as *spermin* (referred to above), which is made from the interstitial cells of Leydig—the essential endocrine cells of the testes—is as essential a part of this formula as any, and is given, naturally, for its general dynamic influence as well as its specific homostimulative influence (already referred to) upon the interstitial cells of Leydig in the individual to be treated.

Treating an Endocrine Complex. Pluriglandular therapy of this type is directed at all the real or prospective causes of a functional hypogonadism. Not merely are the essential Leydig cells stimulated directly, *but the effort is made to modify those factors which may be fundamentally the cause of the hypogonadism,* notably in the anterior—or glandular—lobe of the pituitary and the prostate, while the association of the general toning and cell-stimulating influence from suitable doses of adrenal and thyroid makes a combination that is really hard to beat in the treatment of functional impotence.

However, this treatment, while successful in many instances, fails almost as often, and I cannot refrain from lending decided emphasis to the necessity for careful selection of cases suitable for this method of therapy, and for good diagnostic work.

If local treatment is necessary and is not given, surely organotherapy will not accomplish the desired end. If there is a structural difficulty, as, for example, an organic destruction of tissue, organotherapy cannot be of homostimulative value under such circumstances.

The treatment of impotence, to my mind, involves a good deal more than organotherapeutic stimulation and must

not be expected to render the slightest service when there is a psychic element at the bottom of the trouble or a hidden infection which has been entirely overlooked. Organotherapy is effective in endocrine trouble. When impotence is the result of endocrine insufficiency of not merely the sex glands but of the glands which are responsible for initiating their activities, notably the pituitary, adrenals and thyroid, then pluriglandular therapy is most likely to render results. *Gonad Co.* (*Harrower*) is the most efficient organotherapeutic measure for the treatment of impotence that I have ever seen or heard of. Hence, in cases of impotence, it is very necessary to rule out associated factors that are not of an endocrine character before offering hope from pluriglandular therapy. And too much emphasis cannot be laid upon this aspect of the treatment of such cases.

The Most Suitable Cases. The cases of impotence that respond best to organotherapy are the functional ones that have followed a severe infection, as influenza, severe intoxications, either wilful (drug addicts) or accidental, and the large class in which a developmental factor of unknown origin has interfered with complete functional development of these organs. Sad to relate, there is quite a large class—which includes the senile and the roué—who do not deserve to regain their lost virility, which has been misused, although in these cases organotherapy has been used with results equally as good as those we expect from homostimulative organotherapy of any other endocrine organ that has been functionally overworked and played out, as, for example, the adrenals. The fact remains, however, that just as the alcoholic's liver is most obstinate to the best of treatment, so the gonads of his fast-living associates cannot be expected to live up to the abnormal demands made upon them and may not respond to the best of treatment. The underlying principle of organotherapy, however, remains. Consequently, other things being equal, and provided that circumstances can be made half-way favorable, there is greater hope for the reëstablishment of gonad endocrine function from organotherapy than from all the phosphorus, damiana and nux in the world; for hormone therapy has one great thing in its favor: *it is a natural method.*

Most of the cases in whom *Gonad Co.* (*Harrower*) has been used were old chronic cases who had been treated previously without satisfactory results. I am assured that many of them had long since been given up, and reëstablish-

ment of those factors which are dependent upon normal sex function—general, chemical and reproductive—is just as possible in cases of impotence due to hypocrinism as the reëstablishment of a deficient menstruation following suitable organotherapy, or the control of other dystrophies which may be due to glandular insufficiency. This puts a new and more encouraging aspect upon a subject which is unfortunate, to say the least. Even if we have not found Ponce de Leon's long-sought *Elixir Vitae,* the prospects are better than heretofore merely because we have acquired a broader viewpoint, and are now willing to treat not merely the victims of the circumstances—the gonads themselves—but the associated factors which may be just as responsible for the difficulty. *Gonad Co.* is given in doses of 5 or 10 grains three times a day, usually for some weeks or months. It should be given as a part of the treatment of a given case. Causative factors—infective or psychic—should be controlled, for obviously no form of therapeutics not directed at these could be expected to be resultful.

Treatment of this type should be considered as experimental. It is not always possible to determine in advance whether a given case is purely functional or whether there may not be some organic or extraneous circumstance that will militate against success. One thing is certain: that the broadening of organotherapy by making the right combination of the associated glandular substances is nowhere more obvious than in the treatment of impotence with this pluriglandular formula. To say the least, it is worthy of consideration, especially when both physician and patient usually are decidedly "up against it," as so frequently is the case in such conditions.

SECTION V. CHAPTER 22

INTESTINAL STASIS AND INTERNAL SECRETIONS

Sir Arbuthnot Lane, of London, who has prominently brought forward certain phases of the subject of intestinal stasis, repeatedly has called attention to the frequent endocrine manifestations associated with this common syndrome. These are naturally the result of the absorption of poisons and this toxemia, in turn, is responsible for further endocrine dysfunction which causes certain symptoms and,

at the same time, aggravates the disturbed cellular chemistry, thereby making a vicious circle.

It is well known that moderate forms of hypothyroidism, for instance the so-called *"myxedéme fruste,"* causes a serious cellular infiltration which affects the whole alimentary tract with the rest of the body, thus favoring an atonic and functionally inactive state which speedily becomes a mechanical as well as secretory condition. Attention has been frequently called to the baneful effect of the chronic toxemia of intestinal stasis upon the endocrine organs and especially the adrenal glands.

With this brief introduction in mind, relaxed abdominal walls, visceral ptosis and intestinal stasis must not be considered as purely abdominal lesions of anatomical interest. Mineral oil may be well enough as a remedy; but it does not get far beyond the intraintestinal conditions. Surgery may be well enough, too, but it does not reach much further than the local, anatomical trouble.

The Endocrine Aspect. There is a side to the study of the symptomatology of enteroptosis that should be worthy of attention equally with the strictly anatomical disorder—the undoubted effects of the associated chronic toxemia upon the glands of internal secretion.

There never was a case of chronic intestinal stasis, or Lane's disease, whose hormone production was at par. Pluriglandular insufficiency or hypocrinism is an inevitable concomitant of any prolonged toxemia of whatever discription or origin, just as toxemia is inevitable with intestinal stasis. So in order to do justice to this large class we must also consider the endocrine side of these cases, and in so doing we will assuredly uncover additional possibilities for effective treatment.

Comparatively recently, Dr. V. Pauchet, of Paris, has given this subject some study and in the *Presse Médicale* (April 11, 1918, p. 189) he has demonstrated very clearly that gastro-entero-coloptosis causes a complex pathologic condition including insufficiency of the glands of the abdomen (liver, adrenals, etc.), degeneration of tissue and an unstable sympathetic nervous system. This refers principally to functions which are under the control of the adrenal hormones and accounts for many of the sympathetic manifestations which accompany and are an indirect result of this ptosis. According to Pauchet, persons with ptosis need to be treated for months or years to correct these endocrine disturbances and he recommends hepatic and adrenal

organotherapy as well as a general hygienic régime including physical culture, exercise and massage with an outdoor life, psychic reëducation, etc.

Pauchet then outlines his surgical measures, which do not interest us for the moment; but I will take the opportunity to direct attention to the organotherapeutic phase of this subject and will emphasize its possibilities as an adjuvant measure in the treatment of intestinal stasis. Parenthetically let me say this: Organotherapy often is of service in conjunction with other indicated measures and very rarely is useful alone. In fact, this is really a rule, for in most instances where organotherapeutic extracts or combinations are indicated practically always they should be supplementary to such other treatment as circumstances may direct.

So when the toxemia has reduced the effectiveness of the glands of internal secretion and the ptosis is accompanied by such common symptoms as easy fatigue, severe asthenia, subnormal temperatures, especially in the mornings, malnutrition and the so-called "neuro-circulatory asthenia" (with cardiac asthenia, hypotension and cold extremities, etc.), surely one is justified in attempting to augment the endocrine deficiency by suitable gland feeding.

It is generally admitted that toxemia of intestinal stasis has a greater influence for evil than the mechanical or anatomic factors. It must be controlled by intestinal antisepsis, diet and other indicated treatment. Organotherapy will not accomplish this. Incidentally, among some printed instruction slips which I use in my consultation work, are two which I will reprint here, as they are often quite helpful in this particular connection:

Intestinal Flushing. The lower bowel is often a source of much toxemia and its proper care may greatly help other treatment which may be needed. The high enema, consisting of a quart of lukewarm water in which a teaspoonful of common salt has been dissolved, is an excellent preliminary treatment.

This may be introduced into the colon from a fountain- or bulb-syringe and should be allowed to pass in very slowly and be retained for at least fifteen minutes by the clock, preferably while lying down. During this time it is best first to lie on the back with the hips raised and later on the right side and to manipulate the abdomen gently, commencing at the lower left side, running up to the ribs and down on the lower right side. Often this procedure merely

loosens the easily removed feces and an oil enema is advisable, for the oil gets into the kinks and crevices. This is given with a bulb syringe preferably following the cleansing enema referred to above.

Secure one pint of any vegetable oil—olive, almond or cotton-seed. Place the bottle in warm water until the oil is at body heat, divide the bottle into thirds by marks on the outside, then place one end of the bulb enema outfit into the oil, squeeze the bulb to empty the air, insert the nozzle and slowly inject about one third of the oil into the rectum. The previously mentioned positions should be taken and the oil held in all night (sometimes it is necessary to use a cloth to protect the clothing). Repeat this procedure on the two following nights, noting the amount and character of the stools passed the next days.

In cases of severe intestinal irritation it is an advantage to replace one ounce of the pint of oil by one ounce of isarol (or icthyonat), as this has an antiseptic and soothing influence.

Light Exercises for Strengthening the Abdomen. 1. Lie flat on the back (with bladder empty) with knees bent. Gently stroke the abdomen downward, 6 times, along the inside of the left hip, from ribs to pelvis.

2. Stroke 3 times across the abdomen on the navel line from the top of right hip to top of left, then downward as in (1).

3. Draw the lower abdomen forcibly inward by muscle contraction (not by breathing), and imitate the movement involuntarily made in taking a long, restful yawn—breathe in slowly all the air possible, stretching the trunk and neck forward, then as slowly breathe out all the air taken in, relaxing the body fully. Repeat 6 or 8 times. (This exercise also may be taken sitting or standing and may be repeated often with advantage.)

4. Forcibly draw in the lower abdominal wall (by muscle contraction), then raise it and hold long enough to count ten. Do this three times. Rest and repeat.

5. Repeat the series after becoming accustomed to the exercise, but do not tire yourself. Do not apply pressure below and to the inside of the right hip (region of the appendix).

These exercises should be taken on retiring, to overcome the sagging of abdominal organs due to the standing and sitting posture. They may be repeated half an hour or more before meals, if indigestion and gas are present.

The simple instructions have proved quite helpful and despite their elementary character I find that when they are faithfully put into practice it makes a great difference in the routine treatment

Thyroid and Intestinal Stasis. In a paper in *The Practitioner* (London), for August, 1920, Stiell in discussing the advisability of the removal of the colon for intestinal stasis, asserts that the control of toxemia is a very much more rational method. He states that the administration of thyroid extract is a more reasonable procedure, since in many instances the stasis may be due to an impaired muscular contraction from a chronic myxedematous inflation of the muscles of the bowel wall. Stiell refers to the work of Hertoghe, of Antwerp, who has exhibited dozens of cases of intestinal stasis entirely cured by the judicious administration of thyroid extract, and suggests that the improvement of chronic constipation, headache, and lassitude, which is experienced by a large number of women following ovarian activity, may be due to the stimulating effect that these factors have upon thyroid activity.

I have frequently called the attention of the profession to the importance of this infiltration and have referred to it in many differing and widely separated aspects of medicine. This infiltration of thyroid origin is an extremely important factor in alimentary disorder.

The Thyroid Function Test is Helpful. As has been stated, hypothyroidism is a common concomitant of intestinal stasis. It may be the essential cause of the whole trouble. On the other hand it may be a result of the associated toxemia. No matter whether the thyroid element is causative or resultant, it is well to look into the thyroid aspect of these cases, and especially those whose appearance is sallow, whose circulation is sluggish and who may also be suffering from various dermatoses. Under such circumstances it is helpful to use my Thyroid Function Test, by means of which a fairly accurate estimate may be made of the secretory apathy or sensitiveness of the gland. This is explained elsewhere in this book. When the chart shows a lazy thyroid, surely the best treatment for the stasis would be incomplete without attention to this factor which, by the way, is commonly ignored altogether.

The Frequency of Asthenia. The most common symptom of intestinal stasis is asthenia. The fatigue syndrome may overshadow all the other symptoms. These patients are tired when they get up in the morning, tired all day and

more tired when they go to bed; and the toxemia and other conditions accompanying the tiredness many times have caused such a change in the blood that instead of carrying off the wastes from the brain it is actually irritating the brain cells and insomnia results. It is, in fact, a common finding in intestinal stasis.

As I have emphasized in the first chapter of this section, asthenia is the chief indicator of the presence of adrenal insufficiency; and it happens that adrenal insufficiency is a much more usual result of intestinal stasis than dysfunction in any of the other endocrine glands, though the trouble is so thorough in its bad work that the patient with stasis may have any kind of endocrine disturbance, including the adrenal and thyroid difficulties already mentioned, pituitary, hepatic and, especially, ovarian disorders.

If every patient with intestinal stasis is likely to have a more or less serious hypoadrenia, pains should be taken to estimate the blood-pressure, study the temperature curve, especially in the morning for a few days, and learn the amount of urinary solids, particularly urea. It will be found that practically 90 per cent. of these individuals have low systolic pressure, subnormal temperature and a markedly decreased elimination of solids. In other words, they have the typical syndrome of hypoadrenia which deserves to be considered and treated equally with the alimentary difficulty.

Organotherapeutic Suggestions. A few words about the organotherapy of intestinal stasis are now in order. It certainly is a helpful measure in the treatment of the natural results of alimentary toxemia and stasis. The French urge hepatic therapy as a fundamental method, as it embodies the ideal hepatobiliary stimulant, and in France *"opothérapie hépatique"* is very much more usual than here. They also routinely use adrenal extract in hypoadrenia, and combinations of these glands are used with success. It is indeed good policy to look at this side of these cases.

To tell the truth, most of my ideas concerning organotherapy, and particularly the combining of synergistic gland extracts, came as a result of what I saw and heard during several visits to Paris; and one of these ideas embodied in the formula known as *Hepato-Splenic Co.* (*Harrower*) is worthy of consideration in cases such as Pauchet has mentioned. This formula (No. 5 on our list) contains two grains each of the desiccated extracts of hepatic and splenic parenchyma, one grain of spermin extract which

represents approximately nine grains of fresh Leydig cells (from the testes), one quarter of a grain of desiccated adrenal substance and a twentieth of a grain of thyroid (U. S. P.). This makes a good "shotgun mixture," which, besides encouraging the reëstablishment of the very alimentary functions which are so usually deranged in these cases, supports the adrenal glands and exerts an antitoxic and trophogenic influence of value in modifying conditions so usually untreated in many cases of chronic intestinal stasis. The dose is preferably ten grains between meals three times a day for some weeks, to be reduced later to one dose four times a day for a further period; and *always as a part of a painstaking and persistent therapeutic regimen.*

Biliary Stimulation. Sometimes it may be advisable to institute more active treatment directed at the biliary stasis, in which case the *Bile Salts Co.* (*Harrower*) (No. 22) may be administered in the step-ladder fashion suggested in Chapter 13 of this section. Again, the alimentary paresis may be so severe that nothing short of drastic measures must be followed out, and here it is well to give hypodermic injections of *Liquor Hypophysis U. S. P.* (*Harrower*). I recommended one half a mil. daily or every other day for a week or two. It certainly stimulates the atonic intestinal musculature.

To recapitulate: Study the endocrine aspects of intestinal stasis. Find out if there is an associated hypothyroidism, and treat it. If the bile is deficient, help the body to make more by giving *Bile Salts Co.* as advised. If the intestinal atony is marked use the posterior pituitary principle to initiate the treatment and continue it for a week or two. If there is hypoadrenia present push "the best remedy for adrenal support"—*Adreno-Spermin Co.* (*Harrower*), giving two with each meal and at bedtime for two weeks; then reduce to one, q. i. d. Later, in the majority of cases, the *Hepato-Splenic Co.* contains enough of the adrenal supportive elements plus hepatobiliary stimulants to serve well, and this may be given in place of the *Adreno-Spermin Co.*, and in the same dosage.

The Effects of Secretin. Still another possibility in the organotherapeutic treatment of intestinal stasis is represented by secretin-bearing extracts. There may be a decided deficiency in the production of this alimentary activator, and in cases with gastric insufficiency, hypochlorhydria, and the resultant defective duodenal functioning, *Secretin*

Co. (*Harrower*) has been known to be helpful. The physiology of the hormone secretin and some of its therapeutic possibilities are discussed in a separate chapter in this section and with this in mind special attention is called to some X-ray findings by Quimby following the use of secretin in measured cases of ileac stasis, quoted from the *New York Medical Journal,* July 24, 1915.

SECTION V. CHAPTER 23

THE MUCINASE THEORY IN MUCOUS COLITIS

For a long time it was supposed that the real, underlying cause of mucous enterocolitis was a nervous one, and that the neurasthenia was intimately connected with the causation of this common and intractable condition. Personally I am not convinced that this is so; rather do I believe that the neurasthenia so often accompanying mucous colitis is a result of the combination of conditions—not a cause of it.

About ten years ago some very interesting work on mucous colitis was done in France by Professor Roger and his associates. Like many a really good thing, the ocean seemed to prevent its reaching us in this country, and while in all these years "the mucinase theory" has been put to practical use quite commonly abroad, here it is still the rule to muddle along with our cases of mucous colitis as best we can.

Mucinase and the Coagulation of Mucin. Briefly, the idea is this: The intestinal walls normally secrete a ferment named by Roger "mucinase," a function of which is to coagulate mucin. This ferment is rendered inactive by certain alcohol-soluble, heat-stable substances in the bile, and Roger inferred that, since the disease was so often associated with biliary insufficiency and experimentally produced by diverting the bile flow from the duodenum, the membrane formation was due to insufficiency of bile. Later Riva actually isolated and identified mucinase in the feces of patients with this disorder. Nepper and others have proved this both clinically and experimentally, and Nepper has come to the conclusion from his clinical results that mucous colitis is due to what is called *"oligocholia"* (bile insufficiency) and cannot exist without it, and that the membrane

formation is due to the abnormal increase in the ferment mucinase and to a relative and simultaneous diminution in the production of the bile, especially as regards its anti-coagulating power, which permits the mucinase secreted by the intestinal epithelium to assert its coagulating powers.

All of this explains the following statement quoted from Roger's book on the disorders of digestion: "For those who pass membranes, prescribe an extract of ox-gall, and you will frequently see a subsidence of the pain and a complete disappearance of the membranous casts."

Whether it is true that the bile plays an intimately important rôle in the causation of mucous colitis, or not, is a matter of technical interest. We know full well that the production of mucus, the resultant intestinal irritation and toxemia, and the final tenesmus and discomfort during the "spells" of loosening the bacteria-ridden mucous poultice which covers so much of the intestinal area, and the general malaise are always accompanied by symptoms attributable to hepatic torpor and biliary insufficiency. I do not recall ever having seen a case of mucous colitis where I felt that the production of bile was normal.

Many patients with colitis need cathartics during the periods which intervene between their "spells," and all of them are toxic and have a very foul alimentary condition. If, instead of having recourse to the usual cathartic remedies, we would use "the most natural cathartic known"—bile—we might be doing something of direct physiologic service to the patient, for in addition to its chologogue and cathartic value, the bile carries with it a subtle something that neutralizes the ferment which favors the coagulation of mucin.

A Routine Method of Treatment. This is not a theory; for it has been put to splendid use in practice and I am going to suggest a routine method which may stand many of my correspondents in good stead in some chronic case which has "been the rounds" with little or no help:

First clean out the bowel by judicious catharsis, a very limited diet for a day or two, cleansing enemata—sometimes a hypertonic saline enema loosens the mucous nicely—and the use of high oil injections (four ozs. of cottonseed oil preferably, containing 10 per cent of Isarol) to be retained all night for, say, three nights in succession. Administer generous doses of your favorite intestinal antiseptic—the sulphocarbolates, iodin in proper form, bismuth betanapthol or salol—and get a decent start.

Then prescribe a non-toxic diet with the easily putrefiable proteids reduced to a minimum (no bran, cellulose or mechanical irritants) and the known-to-irritate foods (all these cases will tell of some special foods that cause unusual trouble) eliminated entirely.

Then give bile and encourage the hepato-biliary function to the limit. I suggest No. 22, *Bile Salts Co.* (*Harrower*), each dose of which contains three grains each of repurified powdered biliary salts and of desiccated hepatic parenchyma. Give in stepladder doses as follows: Prescribe one 6-grain dose three times a day between meals for two or three days, then increase by adding an extra one to the last dose, then still another dose until the patient at the end of a couple of weeks is taking, perhaps, three, three times a day. The signal to reduce the dosage is the presence of free bile accompanying the stools, and the patient should be requested to watch for the yellow-green bile floating upon the water in the toilet. When this appears, irrespective of the amount that is being taken at that time, reduce the dose to the original one, three times a day, and start up the ladder again, either at the same rate (increasing the dose every 2 or 3 days) or at longer intervals. Have this procedure continued for several months, or modify it as suggested below, the while giving the patient some acceptable form of *B. bulgaricus*. (I have been in the habit of prescribing a very active and convenient fresh culture made by the Vitalait Laboratory of Pasadena—they send it out twice a week in tubes and charge for it by the month.)

The Relation of Secretin to Mucous Colitis. There is another angle to the subject which should be mentioned. While the Roger-Nepper idea is sound and practical, it may occur to us to question why there is a biliary insufficiency, with corresponding reduction in the production of mucinase, etc. There are several fundamental causes, one of the chief of which is gastric indigestion with deficient production of hydrochloric acid and a consequent defect in the production of secretin in the duodenum. This is a serious matter, for it has been shown that secretin activates pancreatic digestion, the functions of the intestine itself *and also the production of bile.* Hence duodenal extract (secretin) may be equally as effective as bile salts, and, perhaps, even more fundamental in its influence than bile alone. It happens that *Secretin Co.* (*Harrower*) (No. 15) also contains a dose of bile salts as well as an effective amount of adrenal substance—and hypoadrenia is about the most common result

of mucous colitis due to the invariable toxemia which naturally depletes the adrenals.

So one has the choice of these two preparations in the organotherapeutic part of the treatment of mucous colitis, and it is difficult to say which is most efficacious. I recommend the *Bile Salts Co.* in the stepladder method suggested for, perhaps, a month, and then the continuation of the treatment with *Secretin Co.* for a month or more. Both may be taken together, the dosage being regulated by the effects of the total amount of bile that is given daily. The fundamentals of the physiology of secretin and some remarks about its therapeutic possibilities will be found in Chapter 24 of this Section.

SECTION V. CHAPTER 24

STARLING'S "ALIMENTARY HORMONE"—SECRETIN

In 1902, Prof. E. H. Starling, of University College, London, announced the discovery of what has been called "the original hormone." He named it *secretin* and established the fact that its essential function was to activate the pancreatic enzyme precursors. It appears that this was the first internal secretory product to be studied in an accurate manner, and Starling coined the term *"hormone"* (from the Greek, "I arouse, or set in motion") to designate the class of "chemical messengers" of which the newly discovered secretin was the type.

The Origin of Secretin. Secretin is produced in the cells of the duodenal mucosa, and, unlike the duodenal secretion, is passed into the blood rather than into the alimentary canal, and by humoral passages reaches the pancreatic cells and there combines with protrypsinogen and other half-formed enzymes. The secretin becomes an actual part of the finished cell product. It is a true hormone, and in the past eighteen years has been shown to have a much larger range of physiological activity, as well as to be an agent of considerable therapeutic merit in furthering deficient functions of the character that this hormone is known to activate.

Much criticism fell upon Starling and his co-workers, especially by the Russian school headed by Popielski, who felt

that the grandeur of the then recent work of Pavloff on the "appetite reflex" had been unwarrantably dimmed. As a matter of fact, Popielski failed to show that there were any nervous impressions involved in the hormonic effects of secretin, and some years later Hustin, of Brussels, clinched the matter beyond all peradventure by activating the production of pancreatic juice by a canine pancreas lying in a paraffin bath, the dog having been destroyed previously. I, myself, know of this beyond doubt, for I had a chance to work with Hustin in his laboratory at the Institut Parc Léopold, while a method of proving the activity of secretin on the isolated pancreas was being developed.

Hallion and Enriquez, of Paris, showed conclusively that secretin-bearing extracts from duodenum stimulated the duodenum itself to greater secretin production, as well as its other functions. The administration of secretin causes an increased blood supply to the duodenal mucosa and actually increases the secretin content of the cells by test.

The Therapeutic Value of Secretin. Still later, Beveridge, of New York, showed that secretin exerted a subtle influence, direct or indirect, upon the protein-digesting capacity of the blood cells, and emphasized the value of secretin-bearing extracts when given by mouth. Secretin has since been found to have an extended influence upon alimentary functions as a whole and particularly upon the liver. It was proved that duodenal extracts exert a chologogue influence equally with bile, but in a different manner. Perhaps the most recent work on this subject is that of Eddy, of Montreal (*Am. Jour. Physiol.*, March, 1919). He and Downs conclude that "the amount of bile is increased by secretin."

The subject was fully outlined by me in a paper published in the *New York Medical Journal* as far back as August, 1913, and considerable interest in the possibilities of this remedy was aroused. This article was considered of sufficient importance to be translated into German by Professor Boas, and published in his *Archiv für Verdauungs-Krankheiten.* In this paper, the following conclusions were made:

(1) Secretin is a specific excitant of all of the important digestive juices—pancreatic, gastric, hepatic and intestinal.

(2) It may be given by mouth with good results in the large class of gastro-hepato-intestinal disorders described under the general head of "digestive insufficiencies."

(3) Such medication is absolutely physiological, as in certain cases it seems that secretin is a necessary substance which the body is not supplying in its normal amount.

(4) Secretin is not a digestant, having no influence whatever comparable to the commonly used ferments, pepsin or pancreatin.

This work has been the subject of considerable criticism, and some experimentalists have shown conclusively (upon normal or anesthetized dogs, rather than by clinical tests on patients with alimentary insufficiencies) that secretin by mouth is inactive and that dry extracts of the duodenal mucosa, such as are used in medicine today, do not contain secretin. Yet for nearly ten years physicians in France, Italy, England and the United States have continued the use of duodenal preparations with what they have believed to be good results—results which have shown themselves superior to those following other methods of controlling digestive deficiencies, especially in chronic cases where other measures have been tried fruitlessly.

Influence of Secretin on Nutrition. In discussing the therapeutic possibilities of secretin, Kingsley (*N. Y. Med. Jour.*, July 24, 1915) called attention to the fact that many attempts had been made to use secretin in diabetes because its characteristic action on the pancreas was supposed to extend beyond its well-known enzyme-stimulating effects and to increase the internal secretory powers of this gland. It has been used in a number of cases of diabetes, but almost universally had no effect upon the sugar in the urine. On the other hand, diabetics using it gained in weight from 10 to 20 pounds and were greatly improved in general health. It was hard to reconcile these two observations, and an explanation of the good results is found in Beveridge's paper, which was under discussion, which tells of the favorable action of secretin on protein metabolism and in relieving intestinal stasis and the accompanying toxemia.

The Physiology of Digestion. A word or two about the physiology of secretin in digestion will be helpful in establishing the importance of duodenal preparations in therapeutic practice. It is proved that the acid chyme (or HCl) passing from the stomach is the key which unlocks the duodenal cells and liberates the secretin. If there is achlorhydria, obviously there is little or no secretin, and consequently pancreatic indigestion ensues, with its typical intestinal findings. If acid, (lactic, hydrochloric or even tartaric) is administered to such cases in a capsule which is insoluble in the stomach, the solution of this acid in the upper intestine will partially take the place of the missing gastric acid and release some secretin, at least. In all cases of gastric in-

sufficiency—achylia, hypopepsia, cancer (local or general) and "gastric asthenia"—the urge to liberate secretin and thereby activate the whole digestive cycle is reduced or missing.

Secretin is a stable, chemical substance which is evidently not entirely destroyed by the digestive ferments or acids, despite a few statements in the literature, hence to give it is to "set in motion" a chain of physiological circumstances of equal importance and comparatively similar to the administration of thyroid extracts in hypothyroidism or any other form of homo-stimulative organotherapy. Carlson, of Chicago, denies the efficacy of secretin in therapeutics, and derides me for my opinions; yet since his paper was published I have used secretin products for years and cannot disbelieve my own experiences nor deny repeated statements made to me by other practicing physicians. One of these, a famous gastro-enterologist, whose book is well known, told me personally, after publication of the paper, herein mentioned, with its hard and fast conclusions that my statements and those of others "ran contrary to well-established experimental facts," that he had practiced his specialty for over twenty-five years, and that he had never found as active digestive stimulants as the secretin preparations—he had used two kinds—and that he spoke from personal as well as from clinical experiences. I prefer to believe a practical clinician in anything of this character.

Clinical Reports in the Literature. There are a number of statements in the literature (and, by this time, in several of the text books) speaking favorably of the therapeutic value of duodenal extracts and secretin. Beveridge summarizes his clinical findings (*N. Y. Med. Jour.*, June 26, 1915) as follows: (1) Secretin is indicated in all pancreatic insufficiencies where true organic changes have not occurred. (2) It may be employed to advantage in aiding protein digestion. (3) It is a most important factor in raising a low urea output to normal. (4) It is indicated in gastroenterostomy and jejunostomy. (5) It is of distinct value in nephritis of intestinal origin. (6) It increases peristalsis and is indicated in all cases of stasis.

A. J. Quimby examined a number of Beveridge's patients with the X-ray and stated that the impressions of the value of this measure were gratifying. In some of the worst types of stasis, practically no iliac stasis existed and the colon delay was materially reduced. He remarked that "having followed with interest the progress of the several

patients who were examined by the X-ray during their treatment with secretin, he had been pleased and astonished at the remarkable improvement" (*N. Y. Med. Jour.*, July 24, 1915, p. 217).

In the same discussion, W. E. Fitch said that notwithstanding the contention of some authorities to the contrary, his personal experience had completely convinced him that secretin was a potent remedy when administered by the mouth. For about a year he had suffered from intestinal stasis, and the symptoms had been completely relieved by its use. When he stopped taking it he found that the symptoms returned, but, after taking it again for several days, these entirely disappeared. From his own experience, therefore, as well as from his observation of its effects on others, he "was an enthusiast for secretin."

With these reports, old and new, experimental and clinical, in mind, what shall we say then about the availability of duodenal extract in gastro-intestinal secretory insufficiencies, with their numerous baneful results? I say this: Secretin, i. e., suitably prepared desiccated duodenal scrapings, is well worth a trial, for it has served well heretofore and it may again!

Reinforcing Duodenal Extracts. The desiccated duodenal extract may be combined with a useful dose of active bile salts which admittedly stimulate biliary secretion, and hence are likely to be of reinforcing value in practically all forms of alimentary insufficiency for which secretin has been recommended. Further, since the adrenal glands play such an important part in the regulation of alimentary tone, both muscular and secretory, and some prominent French physicians have gone so far as to classify a definite form of indigestion as "adrenal dyspepsia" and recommend adrenal therapy for it, the addition of a suitable amount of adrenal substance is in order, the more especially as chronic digestive troubles are commonly accompanied by hypoadrenia with its cardinal symptoms of asthenia, hypotension and deficient oxidation.

Usual Indications. To conclude, I recommend *Secretin Co.* (*Harrower*) (No. 15) as an adjunct to the usual eliminative, dietetic and hygienic treatment of alimentary insufficiency, which manifest themselves as dyspepsia; gastro-intestinal fermentation and putrefaction; hepato-biliary, pancreatic and intestinal indigestion; constipation; stasis and chronic malnutrition of digestive origin. The dosage is somewhat indefinite. In most cases, two doses between

meals suffice, and this is recommended to begin with. After two or three weeks, it may be reduced. Occasionally still larger doses may be used for a short time. It must be remembered that this is not a ferment preparation and its ingredients do not act locally upon the mucous membrane of the digestive tract and that its principal function is to facilitate the reëstablishment of a deficient secretory function just as we expect glandular stimulation from any other phase of organotherapy. In whatever dose it may be given, it should be remembered that associated treatment is indicated, i. e., that *Secretin Co.* does not take the place of dietetic regulation, alkalinization, the removal of accumulated alimentary wastes, etc., and further, that the effect of this, as of other forms of organotherapy, is of a reëducative character, hence should be continued for some time.

SECTION V. CHAPTER 25

THE MINERAL SALTS IN HEALTH AND DISEASE: REMINERALIZATION

The metabolism of the mineral salts is at once one of the most difficult puzzles and one of the most fascinating studies in human physiology, and has been the subject of much discussion for many years.

The mineral part of the body, as of the food, is fully as important in the nutritive process as the other better-known elements. The minerals used by the body are by no means merely concerned in maintaining the cell structure, especially of the bones, but investigation of the methods whereby the body renews itself and antagonizes the toxemia of health and disease discloses a phase of mineral metabolism represented by a continued struggle between acids and alkalies. "Acidity spells death—alkalinity life," for after death the alkaline reaction of the blood and body fluids is lost, while on the other hand alkalies very often serve to stave off the tendency to acidemia, which is one of the grim reaper's most effective weapons.

Crystalloids and Colloids. The essential rôle of the inorganic elements of the body is not fully understood, and much discussion has centered around the "crystalloids"—salts of an inorganic and non-physiologic character which pass rapidly through membranes and therefore are not easily re-

tained by the body—and the "colloids"—mineral salts which have been so changed that they have acquired an organic character and are not now crystalline but semigelatinous and diffusible. It appears that the normal salts in solution in the fluids of the body are identical *chemically* with similar inorganic salts of like molecular makeup, yet *physically* they are different, the permeability just mentioned causing a difference which enables the body to use and retain colloidal salts without their being carried off by the emunctories, while the crystalline salts are speedily dissolved and eliminated. How the crystalloids metamorphose into colloids, and what the difference is between, say, the potash salts in vegetables and potash dug out of the earth, is not known.

It may be of interest to recall, in this connection, that spleen, which is a hematinic, is supposed to exert a "colloidogenic" action, i. e., it favors the maintenance of the mineral salts of the body in their colloid, organic state and thus prevents this so-called "demineralization"; and, to mention only one other point in this brief statement, according to Schiff, this organ (and extracts of it) favor the "fixing" of iron by the cell.

In certain diseases there develops a tendency toward mineral starvation—"demineralization," as the French call it—and in tuberculosis, perhaps the best understood of these, Robin has shown that the tissues seriously lack these minerals, lime, phosphates, etc.) and also that the urinary output of these substances is greater than urinal. Endocrine dysfunction favors mineral deficiency because of the slowed and disturbed chemistry resulting from the lessened hormone stimuli which are necessary to maintain metabolism at its proper speed. The wastes which are not fully oxidized are many of them of acid nature and neutralize the body's reserve of alkalies, and bring about the condition known as "demineralization." Just as soon as there is a deficiency in this alkaline mineral reserve a further improper functioning of the ductless glands is favored. In some instances they may be irritated by these poisons, but in most cases their function is lessened—they are overburdened. It is difficult to determine just when cause becomes effct, and *vice versa;* but insufficient activity of the endocrine glands and demineralization, or a lessening of the body's reserve of alkaline salts, are intimately related to one another, and from a clinical standpoint, should be considered simultaneously. In certain endocrine disorders (of the ovaries, para-

thyroids and thymus, to mention those most studied and discussed in the literature) serious changes in the mineral metabolism result, and the administration of certain salts, notably of calcium, may be of noteworthy therapeutic benefit.

Bayle, of Cannes (*Revue de Méd.*, Paris, 1911, xxxi, p. 482), believes that the spleen has a "colloidogenic" function—that of transforming easily lost crystalline salts into colloids which can be retained, and the prevention of a pathological change of the colloids with their subsequent automatic loss to the organism. He has given spleen extract on this basis and asserts, from the nutritional standpoint as well as from laboratory experiments, that whether his "colloidogenic theory" is sound or not, it works in practice.

The Importance of the Alkaline Reserve. Much controversy has developed over the question of the availability of the mineral organic salts so often prescribed, and, as usual, certain laboratorians seem to deny the right of the clinicians to draw their conclusions. While the opinions still differ exceedingly as to the acceptability of these salts by the body, clinical experience indicates several important points which may be reiterated here:

First, the normal and abnormal wastes of the organism are either actual acids (such as lactic, carnic, indol-acetic, oxybutyric, etc.) or of an acid nature (as indican or potassium indoxyl-sulphonate)—and they combine with and neutralize the alkalies of the blood and tissues. They are "alkali robbers" and seem to make no distinction between the alkalies, whether colloid or crystalloid. It is well known that a certain reserve of alkaline salts is necessary to normal physiology and that among many functions which might be mentioned, the oxygen and carbon dioxide exchange carried on through the hemoglobin molecules of the red blood cells is only accomplished effectively in the presence of an optimal amount of alkali in the blood. Decrease this reserve, and oxidation becomes materially reduced, more wastes are produced throughout the body, and a vicious circle is immediately formed.

The Frequency of Acidosis. The body is continually fighting acids. Acidosis and acidemia are conditions which may ensue at any time that the alkali reserve is too greatly depleted, and, unfortunately, the tendency is gradually towards acidosis, for "man begins to die as soon as he is born." Ordinarily the balance is well maintained in health, though the tendencies of eating, breathing and living in our

"foolish civilization" are decidedly in favor of the acid state. We eat large quantities of acid-containing and acid-producing foods, especially the meats; we cook our vegetables in such a manner that the salts are lost; we throw away the best mineral-containing portions of the cereals in our bread, and our methods of breathing and daily hygiene, all the time, favor the depletion of the all-important alkaline mineral reserve. In a study of scurvy (*Jour. Biol. Chem.*, Baltimore, 1918,xxxvi, p. 439), Pitz reports a number of experiments on the influence of meat and various salts upon the development of this serious nutritive disorder, and in his summary he remarks that "these experiments point to a little-emphasized rôle of the calcium salts in nutrition, namely, that of controlling the permeability of various animal tissues and thereby affording protection against invading agents." In this connection, some recent conclusions of Bulman, a Mexican physician (*Gaceta Acad. Med.*, Mexico, June, 1917), based upon the study of lime in physiology and therapeutics, are very interesting. The Indians in Mexico are noted for the preservation of their teeth, even in individuals of advanced age. As soon as they become "civilized" and change their dietetic habits, they develop caries, which is explained by Bulman by the loss of the phosphates and other salts found in the outer part of the grain, which are lost by the fine bolting of the flour. These are needed to keep the teeth strong, especially during pregnancy. This lack of earthy phosphates may result in disease or loss of the teeth. Incidentally, Bulman advises the addition of these salts to the food, especially during pregnancy and lactation, and tells of one sick mother taking them and rickets in her child disappearing under it. The "deficiency diseases," so called, are not by any means due to lack of vitamines alone, but involve the whole of this question of demineralization and remineralization.

We know how common acidosis is, or, as we may now call it, demineralization. It is a serious outcome of diabetes and nephritis. It very commonly follows anesthesia, much research in the last few years indicating that the capacity of the plasma for combining with carbon dioxide is decreased by anesthesia; in other words, anesthesia depletes the alkaline reserve. As a result of this, a generous administration of alkali prior to surgical operations prevents this depletion, increases the factor of safety, and almost entirely eliminates post-operative vomiting—a condition which we now know to be due really to demineralization. Certain

metabolic disorders of children, notably rickets, epilepsy, chorea and general malnutrition, are related so intimately to this mineral deficiency that cases of all these conditions are on record as having been entirely cured by reëstablishing the mineral balance. All of the chronic toxemias, including intestinal stasis, rheumatism, neurasthenia and tuberculosis, to mention a few, have a very large factor of this character; and alkaline depletion, demineralization, lime starvation, or acidosis (as this condition is variously called), are always important factors thereof, and evidently conditions which can be readily modified.

The Influence on the Endocrines. Finally, mineral metabolism is intimately connected with disturbances of function of the glands of internal secretion. Not merely does dysfunction of certain glands seem to cause serious changes in the mineral balance, but since these glands as a whole maintain the tonicity, metabolism and general cellular activity of the body, insufficient endocrine function must necessarily mean a serious change in the alkali reserve. As a matter of fact, this phase of the subject has interested me unusually, for one of the most common associated findings in endocrine disease is demineralization. *Dyscrinism*—deranged endocrine activity—*and demineralization*—depletion of the alkaline reserve of the body—*always go together.* When one is obvious, look for the other. When organotherapy is indicated as a means of modifying disturbed endocrine activity, remineralization is distinctly in order. Take as an example the condition of hypothyroidism, one of the most frequent internal secretory disturbances. The first function of the thyroid is to stimulate oxidation, and the first result of thyroid insufficiency is deficient cell chemistry, poor oxidation and infiltration by the accumulated wastes of the organism. Since these wastes are of an acid nature, we would expect the alkali reserve of the body to be depleted, and this is indeed the case; hence every case legitimately in need of thyroid extract is suffering from mineral starvation. To recapitulate: hypothyroidism means suboxidation; suboxidation means toxemia; toxemia means acidemia; acidemia means alkaline neutralization or demineralization.

Just as sure as the chemistry of the body is disturbed, either by the administration of an abnormal amount of toxins or by the production of an abnormal amount of waste products, so sure does this matter of demineralization and remineralization enter into the case, and I have yet to see an

endocrine case in which this principle was not prominently involved.

Practical Therapeutic Application. What is the therapeutic value of all this? Is it possible to remineralize by the simple use of inorganic crystalloid salts which the organism is not supposed to be capable of "fixing" or changing to the colloid state, especially in disease as a result of which it fails to retain its own essential mineral elements? This is a difficult question to answer in a scientific manner, *but clinically it is easy.* While it may be easier to prevent demineralization than to cause remineralization, there can be no doubt that the administration of suitable quantities of selected mineral salts is helpful in several ways: (1) They neutralize excesses of acid wastes and "one cannot bring about remineralization if there exists in the organism a permanent building up of acids." (2) They thereby spare the organism, or the colloid minerals already in the body or the food ingested, for whether colloid or crystalloid, these alkaline salts immediately and inevitably must combine with these acids. (3) They indirectly favor the work of the detoxicating mechanism of the body, especially that of the ductless glands, by the restoration of the alkali reserves just mentioned. (4) They may indeed be transformed and thereby suited to be stored as the body's reserve through the colloidogenic function claimed by Bayle to lie in the spleen, as already mentioned. (*Progrès Méd.*, Paris, 1913, xxix, p. 530.)

At all events, the administration of "inert" organic mineral salts is not without obvious clinical benefit, whether we can answer the question as to how this is accomplished or not. The correction of this ultimate condition is just as rational as the augmentation of the endocrine deficiency which may have caused it. Remineralization should be the rule in all chronic diseases, especially those which involve metabolism and nutrition. Several methods are available. It is very easy to recommend a package of "Arm and Hammer" brand and to suggest 60 to 100 grains a day in plenty of water, remote from meals. As a matter of fact, half a dozen generous doses of soda bicarbonate with plenty of water is now a routine preparatory measure in many surgical clinics. In France, they use bone dust, oyster-shell powder and other "organotherapeutic" mineral preparations. I do not believe that these salts are any more easily assimilated than the ordinary chemicals of commerce. For instance, dibasic calcium phosphate is actually made from

bone, and therefore, according to some should really be called an "organic mineral" salt.

A Remineralizing Formula. For some time I have used and recommended a mixture of salts which are combined in proportions quite similar to those in the blood. This combination of salts is as follows: Magnesium phosphate, 1; diabasic calcium phosphate, 4; calcium glycerophosphate, 4; potassium bicarbonate, 16; sodium bicarbonate, 25; and sodium chloride to make 100 parts. These correspond quite closely to those found in the blood, though the more strenuous sodium carbonate is replaced by the bicarbonate, which is not so irritable, nor is it so deliquescent. This combination, under the name *Calcium-Phosphorus Co.* (*Harrower*), is the standard diluent in The Harrower Laboratory, taking the place of the usual milk sugar, because it has a distinct therapeutic value, especially in cases where it may be advisable to use organotherapy.

To satisfy a demand which has developed quite naturally, I have had prepared for us a tablet consisting of the above formula without sodium chloride and sold under the name *Calcium-Phosphorus Co.*, each containing one gram (15½ grains); so these salts are now obtainable in convenient form, and offer an effective method of remineralization. Under ordinary circumstances, to an adult one should prescribe three tablets, crushed, with much water (2 glasses is preferable), an hour before food, twice a day for three or four weeks, and thereafter on alternate weeks. Obviously, such salts should not be taken on a full stomach, for the gastric acidity would be partially neutralized and the effectiveness of the alkalies immediately lost. Two doses are more convenient than three, and fully as satisfactory, because of the difficulty of fitting them into the daily routine. Such dosage should be continued for several weeks and later renewed for a week or so each month.

Conclusions. To recapitulate: I firmly believe that a concerted effort needs to be made to study the mineral balance and reëstablish it, just as I have long since urged the study and regulation of the hormone balance. This is best accomplished as follows:

(1) Restore endocrine activity, i. e., support depleted adrenals; replace the missing thyroid secretion, etc., by organotherapy.

(2) Proscribe all foods which tend to produce acids. These need not be named, to save time and controversy!

(3) Prevent alimentary stasis and toxemia, for the

products of intestinal putrefaction are the most prolific sources of alkali starvation.

(4) Increase the general metabolism by exercise, water drinking and hygiene, thereby preventing the accumulation of intracellular wastes which, like all such metabolites, are bound to "steal" a certain amount of the precious reserve.

(5) Impress the importance of the alkaline value of vegetables and the acid value of meats. Potatoes are as rich in potassium salts as any available food. Remember that the usual methods of cooking dissolve out these very salts—therefore baked or steamed potatoes are far superior to boiled. Remember, too, that the absurd notions about the looks of flour and bread have developed a custom of removing from wheat a large portion of the salts which the Creator intended to be used and which are found in whole wheat and whole grain preparations.

(6) Administer suitable quantities of the salts which correspond to those present in the blood—preferably, from my personal standpoint, *Calcium-Phosphorus Co.*

What results can be expected from the association of the remineralizing process with other indicated treatment? Just these: That oxidation is increased, the elimination improved and the well-being very decidedly benefited. It seems superfluous to need to tell what kind of results may be expected, for if a person is demineralized, he needs remineralization just as a starving person needs food; and these minerals are *indeed* foods and not drugs. This routine in our study and treatment of cellular laziness and toxemia is but one single factor. To remedy it is but *a part* of the treatment, but it is indeed a very important part.

SECTION V. CHAPTER 26

RENAL THERAPY IN NEPHRITIS

Bright's disease and other forms of nephritis usually give us the impression that they can only be modified by the simple measures intended to spare these organs and to lessen their work. The kidneys are not supposed to be endocrine glands and consequently many presume that they should not be expected to respond to endocrine therapy.

Despite this, there are a few indications that preparations of an organotherapeutic character have been used in

Bright's disease with what, to say the least, must be considered as amelioration.

Renal Impermeability. There are quite a number of articles in medical literature, especially in the French journals, in regard to the value of renal glomerular substance in the treatment of certain forms of what the French call "renal impermeability". In other words, conditions which are akin to Bright's disease, whether accompanied by albuminuria and casts, or not, may be considered as in the category of renal impermeability. In all of these cases there is a lessened amount of urinary solids. The specific gravity ordinarily is very low and there is, or not, as the case may be, a greater or less degree of albuminuria. The dreaded outcome is uremia.

The feeding of renal glomerular substance in such cases increases the amount of urine very definitely. It also lessens albuminuria of a certain type. If I am asked which type of albuminuria would respond to organotherapy and which would not, I can not answer the question, because I do not know—in advance. In fact, I know of no way to find this out except when an opportunity comes to use treatment of this kind and then if the albuminuria is noticeably lessened or entirely eliminated, we presume that there must be a reason for it connected with the treatment and, on the other hand, if it is not, we class it with those albuminurias of the more serious type which organotherapy cannot reach. It is all very unscientific I know, but what would you do if you had Bright's disease and the doctors had given you up and somebody came along and said that there had been a case in a neighboring town who took some organotherapy and had been benefited? Would you not use the organotherapy yourself? It happens that quite a number of physicians have chosen to do this, not merely in their practice, but on their own selves, and there have been enough results from products of my own laboratory to convince me that suggestions of the French are based upon sound reasoning and experience.

Early Clinical Tests. As far back as 1869, the famous but much-maligned Brown-Séquard expressed the belief that the kidneys produced an internal secretion, and in 1892, with his associate d'Arsonval, reported a series of experiments which show that the administration of renal extract postponed uremic manifestations and prolonged the lives of nephrectomized animals. Prof. Tessier, of Paris, applying the results of a good deal of experimental physiology in

therapeutics, later found that the administration of a glycerin extract of kidney substance, caused a diminution and sometimes complete disappearance of certain serious symptoms, such as dyspnea, headache and vomiting of severe renal affections. It is the opinion of a number of French writers that "favorable results from the use of renal substance may be looked for in uncomplicated cases of nephritis." When cardiac complications have risen, this treatment is not so likely to be effectual. Renaut, of Lyons, believes that preparations of this type constitute one of the most active and effective means of treating conditions that are associated with renal insufficiency. This form of organotherapy was, at the time he was writing (1903), considered to be "better than any means at present known" because "it opens up the kidney incapacitated by the edema of uremia." This writer continues: "This method has the advantage over others in that it reduces in a decided manner the albumin passed by the defective kidneys, at the same time frequently restoring their full activity. It can, therefore, be used to favor the restoration of the epithelia, which, in numerous cases, is histologically possible. No other form of treatment applied in nephritis has been known to do this." (*Bull. d. l'Acad. Med.*, Paris, 1904, Vol. 50, Page 99.)

Prof. L. Hallion, also of Paris, believes that the general fundamental influence of organotherapy is in evidence following the use of renal preparations. That is, an extract of an organ acts especially by stimulating the activity and regeneration of the corresponding cells which may be disturbed. And clinical experience indicates that it is likely that there may be a remarkable influence from this form of treatment, especially in the reduction in a large degree of the accompanying albuminuria. Hallion believes that extracts of kidney substance have the power directly to influence the passage of albumin through the kidneys and others believe that these preparations also play an antagonistic and neutralizing part over certain poisonous substances which undoubtedly are factors in the production of the disorders in question.

I am not prepared to state why the renal permeability is increased nor how the elimination of albumin is sometimes lessened in so remarkable a fashion as has happened following the use of preparations of this kind. I do not think that the glomerular tissue of the kidney contains a hormone, but at least I know that it has been used empirically for

years with satisfactory results. For this reason I am perfectly willing to use it whenever opportunity is offered to me.

Pluriglandular Renal Therapy. *Renal Co.* (*Harrower*) contains the desiccated glomerular tissue of healthy kidneys, to which is added an equal dose of three grains of total pancreas substance for two reasons: Practically all cases of kidney insufficiency have an alimentary factor of greater or less prominence, and it is well known that the pancreas encourages digestion and general alimentary efficiency. The second reason for the addition of this product is that the pancreas is a direct antagonist to adrenal irritability and the toxemia connected with nephritis necessarily keeps the adrenal glands functionally "on edge," and this physiological antagonism to hyperadrenia is an advantage, not merely from the standpoint of the associated high blood-pressure which, as is well known, is quite common in renal cases, but also from the standpoint of the general metabolic imbalance which usually accompanies various phases of Bright's disease.

The use of *Renal Co.* (*Harrower*) in functional renal difficulties is worth while. One cannot expect to soften a hardened kindney, nor to change a serious structural disorder of these organs, but in many cases of Bright's disease of the various types, both acute and chronic, there is a fairly large functional element which the administration of this formula has helped to control in a satisfactory manner.

In addition to the dietetic regulations so necessary in these cases, and every effort to lessen toxemia, I recommend the use of this preparation in doses of from six to eighteen grains, three or four times a day with food. A larger dose in the few serious cases for a shorter time and a smaller dose continued for several months in chronic cases.

An Interesting Case Report. I feel prompted to close this short chapter with a report from a physician in Oakland: "I have had some experience with your preparation, list No. 85, *Renal Co.* (*Harrower*), which may interest you:

"A young married woman, a student at the university, was informed by the physician of the infirmary that she had a very bad mitral lesion with failing compensation. She stopped school and some two years later consulted me, informing me that she was pregnant nearly two months. Within ten days, before she had time to get any relief for the heart, she developed acute appendicitis, necessitating an operation. The nausea of pregnancy had been relieved

before the operation by your *Placenta Co.* While it developed again at the time of operation, it responded within three days to the above named preparation.

"When she was about five months pregnant, her urine showed a very low specific gravity, about one per cent. of albumin, and other indications of kidney embarrassment. Then she was given the *Renal Co.* After its use for two months, together with a regulated diet and rest, the urine shows no albumin, normal spec. gravity, and she promises to go to full term. I cannot help but feel that we owe a good deal to organotherapy."

SECTION V. CHAPTER 27

ENDOCRINE ASPECTS OF OBESITY

To facilitate the answering of literally dozens of questions about obesity of various varieties, I want to dictate a few brief statements of my opinions. These are purely suggestive, and at the outset I must emphasize the necessity for considering this particular aspect of these cases in conjunction with every other possible associated condition and treating the patient as a whole.

Most Frequent in Women. Many of the cases referred to in these queries are women, and a large proportion of them are related in some way to a disturbance of ovarian function. For example, one of them, after the birth of her first child, began to increase in weight and gained sixty pounds in a year; another one, quite similarly, after marriage gained in weight from 150 pounds to 240 pounds in about the same period. In a third case, a girl developed a complete amenorrhea soon after menstruation was established, and by the time she was of age she weighed 190 pounds—height 5 feet, 3 inches. And so on.

All of these cases mentioned, and the majority of the other cases of obesity in women that are related to dysovarism, are typical cases of endocrine obesity. They involve the ovaries, and with them the other endocrine glands, notably the thyroid and pituitary. It is not so difficult to see how these glands became involved. Presuming, for the moment, that the thyroid is involved secondarily, may it not be due to the fact that the abnormal ovarian function occupies the thyroid so unusually that it cannot accomplish its other

duties and there is a hypothyroidism, resulting in a lowered oxidation with a lessened B. M. R., and a considerable degree of obesity?

Just yesterday I saw a girl of fourteen who weighs nearly 200 pounds (height 5 ft., 6 ins.) and whose B. M. R. was —16.6. A few weeks previously I saw another girl of 16 whose B. M. R. was —26, who had also an ovarian disturbance and whose weight was 180 lbs—height 5 ft. 4 ins.

Menopausal Adiposity. There is another form of obesity in women that is connected with ovarian dysfunction and is usually found at or near the change of life, when the natural functional ovarian insufficiency manifests itself. This condition is due chiefly to the removal of the influence of the ovarian hormone to which the body has been accustomed for about 30 years, and like all other endocrine conditions, involves the associated glands. Such an ovarian adiposity practically never is found without involvement of the two glands which are intimately wrapped up with ovarian function, that is, the thyroid and pituitary. In these cases the amount of adeps can be considerably lessened when the dysovarism is modified by indicated organotherapy.

Obesity in Children. Every so often we are importuned about some unusually fat child. The prospects are only fair, however. A very interesting paper by Mouriquand (*Lyon Médical,* Nov. 10, 1920) directs attention to the incidence of incipient obesity in children of obese parents. He also has noted that early inherited obesity frequently precedes diabetes, and calls attention to the fact that in such cases of early obesity diabetes is developed before forty in nearly all cases; that when the inherited obesity does not develop until late, the percentage is only 50 per cent, and when the obesity is acquired the ratio is 15 per cent. This writer urges an effort to modify the parental obesity, and especially in pregnant women. In cases where the endocrine glands show insufficiency, organotherapy is indicated, and Mouriquand refers to a girl at puberty threatened with what was presumed to be the adiposo-genital syndrome, to whom he recommended thyroid, ovarian and pituitary treatment in turn for ten days each, or, as he writes, "the three may be given combined." I prefer the latter plan for reasons which I have explained elsewhere.

Many an obese child is suffering from hypothyroidism; a few of them have a thyro-pituitary dystrophy, and the same fundamental principles and therapeutic measures apply in these children as in adults.

Thyroid Obesity. Certain cases of obesity are due purely to hypothyroidism, though involvement of the associated glands commonly occurs. The proteolytic properties of the body are slowed, the metabolism is very seriously lessened, and there is a natural retention of unoxidized material, much of which seems to be metamorphosed into fat and deposited as such. These hypothyroid patients have the regular signs of thyroid insufficiency already discussed, and in every respect, from the inactivity of the mind or of the sweat glands, circulation or digestion, they are below par.

Endocrine Obesity of Non-Thyroid Origin. Some months ago a letter came to my desk inquiring "whether there is anything in the line of organotherapy that is beneficial in the treatment of obesity except thyroid." In my reply I stated that while, of course, one expects that endocrine obesity usually involves the thyroid gland, it is perfectly true that the deficient oxidation and general cellular laziness which one expects in hypothyroidism favors a condition of sub-oxidation and obesity, and this is the reason that so many patients take thyroid indiscriminately as a remedy for obesity—and sometimes rue it. As a matter of fact, the administration of thyroid gland in cases of obesity is not good practice unless one has definite information that the thyroid gland is responsible for the trouble, and even then the thyroid should be given very carefully and under the closest supervision. The Thyroid Function Test usually indicates the degree of thyroid apathy which, of course, varies very much in different cases. The metabolic rate is uniformly low. The elimination as measured by the urinalysis is always deficient.

The Pituitary Factor. I believe that in many cases of obesity the pituitary gland is equally involved. Undoubtedly, the pituitary is related to obesity, for in a typical pituitary insufficiency (Froehlich's syndrome) there is not merely a functional gonad insufficiency and atrophy of the sex glands, but adiposity to an unusual degree, is the rule. The pituitary aspect of these cases is determined chiefly by the estimation of sugar tolerance, for it happens that in hypopituitarism there is not merely asexualism, obesity and a lowered B. M. R., but the tolerance to sugar, which is arrived at by testing the urine periodically, is very high and sometimes these patients can take 300 to 500 grams or more of glucose without any resulting glycosuria.

Dieffenbach (*Chironian*, Jan., 1915) goes quite fully into the pituitary aspects of obesity. Where the adipose patient

has acquired a high tolerance for sugars one may expect the resultant accumulation of fat. Transient polyuria often occurs in these cases, due, he states, to posterior lobe dysfunction. In such individuals amenorrhea is frequent and anaphrodisia; there is constipation, drowsiness and torpidity. "This pictures many cases of obesity occurring in practice, which do not usually respond to diet and are thus proven to be due to a distinct pathological lesion."

The distribution of the fat is of special interest. Dieffenbach refers to the fact that the countenance becomes plump and gross, and the double chin grows early; the fat seems to favor the waist, abdomen and chest, and, of course, there is impairment of both respiration and circulation, dyspnea, and other symptoms due largely to fatty deposits in the mediastinum and pericardium.

Again, Harvey G. Beck, of Baltimore, has drawn special attention to the distribution of fat in the pituitary types of obesity. Attention has been called particularly to the excessive development of pads of fat on the hips. Beck connects this with anterior lobe insufficiency, and, as a result of organotherapy, in a number of cases there has been an increase in the amount of fat in the upper part of the body, with a corresponding decrease in the fat on the hips, changing the physical contour of the individuals quite materially.

According to Klein (*Therapeutic Notes*, July, 1921), the posterior lobe of the pituitary may be involved with a resulting obesity, which has certain important distinguishing characteristics. There is a well-marked accumulation of adipose tissue in the lower abdominal wall. It is sometimes described as girdle obesity. In such persons this girdle extends from the flanks downwards to the front of the abdomen from the umbilicus to the mons. Of course, these people ordinarily have evidence of obesity in other parts of the body, but according to Klein: "If you can see the girdle you may be sure that there is pituitary involvement."

Confirmatory evidence of the hypopituitaric aspects of obesity is found in a slow pulse, subnormal temperature, lethargy, and intestinal atony. In these cases the sugar tolerance test already referred to is an important differential diagnostic measure, as is also the experimental administration of the posterior pituitary principle hypodermically. *Liq. Hypopysis* (U. S. P.) may be injected in 5-minim doses daily and increased gradually to 30 or even 40 minims. The point of tolerance is indicated when the patient complains of intestinal cramps, and, of course, in such individuals the

blood-pressure should be found to be within reasonable limits before the treatment is given. Klein says the "hypopituitary patients frequently can tolerate 2 to 3 cc. of Pituitrin." I must say here that I have never seen a case of pituitary obesity in which there was not associated with the pituitary factor a well-defined hypothyroidism. These two things go together almost invariably. The treatment, naturally, is to replace the missing pituitary hormone, and we have a formula called *Pituitary Co.* (*Harrower*) for these cases, which is a combination of equal parts of the anterior lobe substance and the total gland, which seems to be more efficacious than either of the two ingredients singly.

In cases with a more marked pituitary aspect the ovarian dysfunction is usually of a more serious and complete type. Quite often these people have a low blood-pressure, are very tired, and have other indications that an adrenal insufficiency complicates matters. A good reason for this would be the natural accumulation of the wastes which would be burned up through the intervention of the thyroid and allied glands, but which remain unoxidized and, like other poisons, serve to play out the adrenals.

The Treatment of Obesity. The treatment of these cases should always include an attempt to reëstablish obviously deficient endocrine activity, and in the first type discussed—obesity in women—I always advise *Thyro-Ovarian Co.* (*Harrower*) for two months at least. In individuals who menstruate, one, three times a day, for ten days, then two, three times a day for the ten days immediately before menstruation, and none at all for the ten days beginning at the onset of the flow. In such individuals the treatment later may be amplified by changing to *Gonad-Ovarian Co.* (*Harrower*)—a similar formula which is reënforced with a generous dose of anterior pituitary substance. In some cases where the evidences of hypothyroidism are very well marked, it is sometimes advisable to increase the amount of thyroid, and may be done by using *Thyroid Co.* (*Harrower*) No. 9 (grs. ½), one dose a day for a week; then two doses a day for a week; three doses a day for the third week; and four doses a day (two grains a day) for the fourth week, omitting it entirely during the fifth week, and then starting up the ladder again; thus finding out from the patient's response what the optimal dosage is, and watching, of course, very carefully not to overdo the thyroid medication. All of this is being done, as mentioned previously, while I attempt to regulate the thyroid-ovarian-pituitary aspects

with either of the two pluriglandular formulas referred to.

In this connection, it is interesting to note that Edward C. Titus, of New York, in his article on the "Modern Treatment of Obesity," (*Medical Record,* Jan. 24, 1920), considers the subject from many of the aspects already referred to. He gives passing consideration to the endocrine side, and says: "In view of the fact that insufficiency of the endocrine system plays so important a part in the etiology of obesity, I have occasionally resorted to administration of various glandular extracts, single or combined, for a short period only, as indicated in the individual case. Thus, I have often employed with benefit thyroid, pituitary, ovarian and other extracts, as well as the combined hormones."

Remineralization. An important point worthy of consideration in this connection has been frequently referred to under the heading *"Remineralization."* (See Sec. V, Chap. 25.) People of the type under discussion all have a remarkably low chemical capacity. They tend to accumulate their own wastes, and since many of these are of an acid nature, they rob the body of its reserve of alkaline mineral salts. It will be found on careful examination that a great many cases of obesity are in various stages of acidosis; consequently when we know that there is an accumulation of these wastes it is proper to supplement the organotherapy with remineralization, which I usually accomplish with a formula called *Calcium-Phosphorus Co.* (*Harrower*), containing magnesium phosphate, calcium phosphate, calcium glycerophosphate, potassium bicarbonate and sodium bicarbonate, combined in suitable dosage, and give three grains powdered, with a generous amount of water, an hour before food twice a day for about a month, and thereafter on alternate weeks throughout the treatment.

These two essential measures—organotherapy and alkalinization—are added to thorough elimination by the bowels, dietetic control and good hygiene. It makes no difference whether one or another of these factors may obscure the real reason for any good results that may be secured. The point is to help the patient to the maximum, and as quickly as possible.

Of course, it must be remembered that there is a form of adiposity known as "exogenous obesity" which is due to external circumstances and not to any endogenous condition. Exogenous obesity is largely a matter of unwise eating and lack of exercise, and must be cared for accordingly. Diet

will not benefit a purely endogenous case—this is a diagnostic measure. Without a doubt, it is possible to have both the endogenous and exogenous forms combined, and organotherapy is but a part of the treatment in any such form of obesity and invariably should be combined with suitable hygiene, diet and elimination.

Obesity is not an easy condition to treat from the standpoint of the internal secretions, but whenever there is an endocrine side to a case with obesity, most assuredly this side deserves consideration and treatment with all the others.

SECTION V. CHAPTER 28

SUGGESTIONS IN SIMPLE GOITRE

The extent of the literature on goitre seems almost endless. Hundreds upon hundreds of papers are devoted especially to the subject or take it up in conjunction with associated matters, and, naturally, opinions differ, and to read 30 or 40 of these papers is to find oneself in a sea of difficulty, not knowing in which direction to seek land.

Definition of Simple Goitre. First of all, it will be necessary to appreciate what is meant by the term "simple goitre." The subject has been given considerable study from the diagnostic standpoint in a previous chapter (see Section IV, Chapters 2 and 3). When the thyroid gland is enlarged and is fairly firm to the touch, not nodular, not especially tender, and not fluctuating, it is probable that the goitre is of the "simple" variety. This probability is emphasized if the patient happens to be a girl at puberty or a woman with a menstrual difficulty, for, as we have seen, there is a very close relationship between the thyroid and ovarian functions.

If the struma, as it is sometimes called, is a part of the syndrome in which symptoms of hypothyroidism clearly are in evidence, we have confirmation of the tentative diagnosis of "simple goitre," for in a majority of cases this condition is associated with hypothyroidism.

It is necessary to assure oneself that the thyroid enlargement is not the beginning of another kind of goitre that is related to excessive thyroid functioning, or hyperthyroid-

ism, and this also is determined by the clinical symptoms which have been fully discussed under the subject of hyperthyroidism (Section IV, Chapter 3, and Section V, Chapter 10).

The Thyroid Function Test. One of the simplest and easiest means of determining the character of an enlargement of the thyroid gland is the therapeutic test. Ordinarily, my Thyroid Function Test suffices. This consists in administering stepladder doses of thyroid extract in a certain routine fashion and depending upon the influence upon the pulse during a period of four or five days for indications as to whether the thyroid is sensitive or apathetic. (The Thyroid Function Test has been discussed in original articles published in the New York *Medical Record* of November 1, 1919, "Clinical Results with a Method of Testing Thyroid Function," and April 16, 1921, "Clinical and Laboratory Tests in Hyperthyroidism," and is given further consideration in Section IV, Chapter 4, of this book.) If the findings indicate the condition known as thyroid sensitiveness, it is probable that the goitre in the case is not of the "simple" variety and that an effort will have to be made to find some cause for the thyroid irritability, which it is presumed may be equally the cause of the thyroid enlargement.

On the other hand, if the administration of the 14 grains of thyroid extract (U. S. P.) which constitute this test is followed by an amelioration of certain symptoms, and the patient says that instead of feeling somewhat uncomfortable during the last day or two, with internal nervousness and feeling, perhaps, of apprehension, they seem to be better during the last days of the test and following it, and especially if the pulse record does not indicate any marked increase—particularly during the third and fourth days of the test, and especially if the pulse ordinarily is somewhat less than the normal and not increased or only slightly so—we may presume that the enlargement of the thyroid is related to a condition of hypothyroidism, and that treatment from this standpoint is likely to be efficient.

An Explanation of Thyroid Enlargement. The relations of the endocrine glands are such that there is a considerable degree of physiologic dependency the one upon the other, and the thyroid gland in particular responds physiologically to stimuli as well as to the subtle call which urges it to attempt to regulate or make up for some related deficiency. In other words, the thyroid gland may be enlarged as a re-

sult of some hormonic stimulation or reflexly as a result of a need for a greater service on its part, to help out some associated endocrine deficiency. It happens that this is most commonly the case in girls and women and that the thyroid gland enlarges itself very often in a well-meant attempt to encourage a fundamental deficiency or gradually waning ovarian activity.

In these cases of simple goitre with hypothyroidism, two therapeutic measures are necessary: (1) to lessen the physiologic call upon the thyroid or to regulate the ovarian insufficiency, (2) to supplement the work of the thyroid and to administer thyroid extract in order to make it unnecessary for the thyroid to enlarge itself so much.

Endemic Goitre. In passing, it is necessary to mention a type of goitre which is of geographical importance. It is believed to be endemic in certain locations because of the character of the drinking water. McCarrison has made very extensive studies in India and has come to the conclusion that many such goitres are due to water-borne intestinal infections. His successful treatment of these goitres depends largely upon measures calculated to remove the offending bacteria (which are supposed to be ingested in the food or water) and artificially to increase the immunity to these organisms by means of suitable vaccine therapy.

On the other hand, many interesting items have slipped into the literature regarding a presumed chemical cause for this particular form of "simple goitre." David Marine, formerly of Cleveland, has done a lot of splendid work in the "goitre belt" of Northern Ohio and has studied literally thousands of school children affected with goitre. He has come to the conclusion that there is a deficiency of iodin at the bottom of the difficulty and, naturally, suggests suitable iodine therapy both as a prophylactic and a therapeutic measure. Marine recommends a varying dosage of a saturated solution of sodium iodide—30 grains given in 3-grain doses daily to each school pupil in the 5th, 6th, 7th and 8th grades, and 60-grain doses, given in 6-grain doses each school day, for pupils in the 9th, 10th, 11th and 12th grades; to be given twice annually about the first of May and December. Incidentally, Marine remarks that they have also used syrup of hydriodic acid or syrup of ferrous iodid in 1-mil. doses daily for two or three weeks, repeated twice annually.

In this connection it is interesting to note a little item that appeared in one of the Swiss medical journals in regard

to the existence of endemic goitre in the Canton of Aarau. Here, in a certain village, were quite a large number of individuals with "simple goitre." They all lived on one side of the town, whereas the permanent inhabitants of the other side seemed to be unusually free from this difficulty. Careful investigation disclosed the fact that the goitre-free persons were in the habit of securing their salt from certain outcroppings and on investigation this salt seemed to be particularly rich in iodid—quite an interesting coincidence.

The treatment of the endemic type of simple goitre happens to be quite similar to the treatment of other forms of simple goitre, as we shall shortly see.

Suitable Organotherapy. When the thyroid or any other ductless gland is not working sufficiently, and we have some form of hypocrinism, obviously the best treatment is the judicious administration of the missing substance. Many hundreds of cases of goitre can be cured with thyroid extract alone, though many hundreds of others will do better if dependence is not placed entirely upon the one single, likely-to-be-useful measure. We have seen that many of these people can be benefited by the administration of certain forms of iodin, and for years I have been in the habit of combining a suitable dose of the ferrous iodid with a quarter-grain of desiccated thyroid extract and suitable doses of nucleinic acid for its general cell- and especially white-cell, blood-stimulating influence. This formula, known as *Iodized Thyroid Co.* (*Harrower*) was developed in the treatment of quite a number of cases of "simple goitre" and has come to be depended upon by a number of physicians, many of whom have had an opportunity to compare this with the administration of thyroid extract alone and to conclude, in many instances, that it is superior.

I am not averse to the use of iodin externally. I have sometimes used an ointment of the yellow oxide of mercury, or again, more commonly, "Iodex" ointment, and have advised the gentle rubbing of a small portion of about the size of a Lima bean into the skin above the thyroid each night. Sometimes, in suitable cases, where there is a noticeable ovarian aspect, it has been my custom to modify the location of an inunction of "Iodex" ointment, with or without methyl salicylate, using a portion about the size of a Lima bean, which is rubbed into the skin of each side of the abdomen corresponding to each ovarian area every night on retiring.

Supplementary Organotherapy. Attention has already been called to the importance of the ovarian aspects of these cases, and where the "simple goitre" has originated in connection with disturbed ovarian function, manifested by amenorrhea, dysmenorrhea, or other related ovarian findings, the greatest success will be had by the application of a treatment that is directed not merely at the thyroid but also at the ovaries, and in these cases my routine is to administer *Thyro-Ovarian Co.* (*Harrower*) in the stepladder fashion already referred to (see Section V, Chapter 5), for at least three months, in connection with the "Iodex" treatment just referred to. Later, if the diminution in the size of the goitre is not complete, or, if it has seemed to reach an apparently irreducible minimum, I have found advantage in combining the *Iodized-Thyroid Co.* with the *Thyro-Ovarian Co.* (*Harrower*).

Goitre in the Male. Fortunately, thyroid enlargement is not so frequent in men as in women, though, unhappily, it seems to be a more complex affair; at least, the results from presumably indicated treatment are not usually so rapid and spectacular. The same fundamental principles apply, however, and the treatment with *Iodized-Thyroid Co.* (*Harrower*) and local inunctions are recommended. In my personal experience a higher percentage of men with thyroid enlargement had with it evidence that the pituitary was involved than in women; in other words, a larger number of the thyroid cases in men also had hypopituitarism, in which case pituitary therapy had to be added to the thyroid. I recall two cases of goitre in men that were very successfully treated by the use, first of *Iodized Thyroid Co.* and, later, a combination of this formula with *Pituitary Co.* (*Harrower*) (No. 47 on our list), one of each, 4 times a day.

SECTION VI

ENDOCRINE QUERIES AND ANSWERS

As Director of The Harrower Laboratory, I am requested every day to answer from ten to thirty letters asking for information and suggestions in regard to various endocrine puzzles. Occasionally an answer of necessity must be fairly comprehensive and obviously of interest to many others than the one to whom it was directed specifically. Therefore some of these answers have been worked out a little bit more fully and published in "The Organotherapeutic Review" for the good of as many of its readers as may be interested.

A collection of these queries, carefully arranged and edited, constitutes this section, which it is believed will be a very welcome and practical feature in this new edition.

It should be understood that my answers are suggestive—not intended to be comprehensive or exhaustive—and, naturally, often refer to the work and products of this institution. In the passage of years, the correspondence which comes to my desk indicates that the answers to some of these questions have proved, often in many instances, to be entirely satisfactory; in other words, they have led the way to results.

1. ARSENIC AND THE ADRENALS

Query: "Several years ago I remember reading a statement by Sajous that arsenic depressed the adrenal functions. Is this upheld by later work, and in this connection what about the intravenous injection of iron cacodylate with some preparation of the adrenal gland by mouth? Would a combination of this kind be logical in a tubercular patient?"

Answer: I am not at all sure that arsenic really depresses the adrenal function; as a matter of fact, all poisons stimulate the adrenals merely because it is the function of the adrenal glands to regulate the reaction of the body to toxemia, and of course any amount of a preparation like arsenic is really a poison. I have not read any modification of Sajous' opinion, but he is a well-balanced man and I am not so disposed to quarrel with him as has been the habit

of some. At all events, when the conditions are such that you want to give cacodylate of iron and a tuberculosis is associated with them, certainly the adrenal glands have been overworked, probably are depleted, and, therefore, need support. I think your idea is sound, and if your patient is "all run-down," asthenic and anemic, and you have in mind to use the cacodylate of iron, I think it would be good policy to give the *Adreno-Spermin Co.* (*Harrower*), one q. i. d., also. Or, better still, No. 68 on our list, *Spermin-Hemoglobin Co.*, because it is a combination of the above formula with hemoglobin for use in asthenic anemia. The only contraindication to this, is in those cases where there is an unusual degree of sympatheticotonus, due to the irritation of the thyroid gland by the toxins of the condition which we are attempting to treat.

2. FUNCTIONAL HYPOADRENIA — SERGENT'S TEST

Query: "I have a case of a women, generally asthenic, with low blood-pressure, but Sergent's white line is absent. There appears to be no ovarian dysfunction. What would you suggest for this case? Do you consider Sergent's test reliable?"

Answer: The general asthenia and the low blood-pressure points strongly to hypoadrenia. Probably the elimination of the urinary solids, and especially the urea, is below normal, and the woman has other manifestations of muscular atonicity, as, for example, cold hands and feet, intestinal sluggishness, and perhaps ptosis, and general functional tiredness.

The dermographic sign which was developed by Emile Sergent, of Paris, and called *"la ligne blanche surrénale"*—the white adrenal line—is not to be expected in functional cases of the degree of severity mentioned in your inquiry. The white adrenal line is found in Addison's disease, and serious degrees of adrenal insufficiency considerably worse, I should imagine, than the condition present in your patient. The treatment of a case like this certainly calls for adrenal support in the usual fashion. I know of no better combination for a case like this than *Adreno-Spermin Co.* (*Harrower*)—adrenal substance, a small dose of thyroid, and spermin, with calcium glycero-phosphate as the excipient. I would give the patient one dose at each meal and at bedtime, or four a day, and would continue it for a minimum

of six weeks; longer would probably be better, depending upon the length of time that the patient has been suffering from this condition. The more chronic and long-standing the condition, the longer the necessity for continuing the organotherapy.

In answer to the query as to whether I consider the Sergent test reliable, it is indeed a valuable confirmatory test in severe adrenal insufficiency, principally the organic type, or Addison's disease. One cannot expect to find it in the simple functional hypoadrenia so common in every-day practice.

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3. ATYPICAL AMENORRHEA—THYROID ORIGIN

Query: "In a case of amenorrhea with retained menses, the interval varying from one to three, or even four, months, with occasional menorrhagia lasting as long as twenty-six days within one calendar month, what would be your method of treatment? Fibroids and disease of the adnexa have been excluded. What is the diagnosis?"

Answer: When an individual within the normal menstrual age has menstruated with fair regularity at fairly normal periods and then begins to drop a few days, a week, or a month, or, as in this case, two or even three months, unquestionably there is some imbalance in the mechanism which determines menstruation. This has been called in the title, "Atypical Amenorrhea," merely because this is the title given to it by the correspondent. As a matter of fact, it is not "atypical." Amenorrhea in one person is practically never like the same condition in another person, and there are all shades and degrees of this difficulty.

When the patient has an alternation of a more or less long period of amenorrhea with a severe menorrhagia such as is referred to—lasting twenty-six days—one is immediately reminded of a severe degree of hypothyroidism.

This gives me an opportunity to emphasize a particular point in regard to the relation of thyroid insufficiency and the menses. It is well known that hypothyroidism tends to cause amenorrhea merely because the thyroid hormone has as a part of its important work the stimulation of ovarian function and the initiation of menstruation as a result of it. Therefore, many cases of amenorrhea are of thyroid origin, and it is for this reason that thyroid is often given in conjunction with ovarian substance as a means of regulating a dysovarism manifested by amenorrhea, etc. The

same thing applies in regard to pituitary, and our preparation, *Thyro-Ovarian Co.* (*Harrower*) which contains thyroid, pituitary and total ovary, is given for this purpose, and for these valid reasons.

Now to explain the reason why a hypothyroidism can cause amenorrhea on the one hand and a serious menorrhagia on the other. If the hypothyroidism is a cause of an ovarian insufficiency, we have a perfectly good explanation for the amenorrhea, but if hypothyroidism causes cellular infiltration—the typical manifestation of myxedema, it will be recalled—and if this infiltration involves the uterine musculature, there may be a resultant mechanical factor which will prolong an otherwise normal flow. For this reason those who have studied hypothyroidism frequently call attention to the fact that hypothyroidism may cause amenorrhea, and in other instances may cause quite a serious menorrhagia. The regulation of the dysovarism may benefit either the amenorrhea or the menorrhagia.

The treatment of these cases involves the regulation of the ovarian dysfunction with, I should say, *Thyro-Ovarian Co.*, or, if it is preferred, a special effort should be made first to determine whether thyroid insufficiency is present by means of my Thyroid Function Test.

4. STUNTED GROWTH—JOINED EPIPHYSES

Query: "Which of your preparations would help a boy of 15 who is not deformed but who has only attained the height of an average child of 10?"

Answer: *Antero-Pituitary Co.* (*Harrower*) is a growth and developmental stimulant. It is given in all forms of developmental dystrophies, and, for a boy of 15 who is dwarfed but not malformed, I would give five grains three times a day for four out of every five weeks for a minimum of six months. In cases of this kind, if there is a possibility that the boy has attained his maximum growth and therefore may not respond to organotherapy, it is possible to make an X-ray picture of the hand and note from it if the epiphyses are joined or not. If they are joined completely, the chances for growth obviously are not good; if they are not joined, there are indeed very good possibilities of increasing the height. I have seen as high as four inches added to the stature in less than a year from this treatment, and in a boy of 15 too.

A report came to me not long ago from a physician in

Portland, Ore., about a case of a young man of 18 whose height at the beginning of treatment was 4 ft. 6 in. It seemed advisable to use organotherapy, and *Antero-Pituitary Co.* (*Harrower*) was given in the usual manner. During the first month the patient is said to have grown 3/16 of an inch, during the second month almost half an inch, during the third month there was apparently no change, but in the fourth month the total additional increase was ¾ of an inch. During this time he also gained in weight and the parents are quite delighted with the change. As I have said, ordinarily one cannot expect much in the way of growth stimulation after the usual time of puberty since ossification of the epiphyses is completed soon after that time.

5. HYPERTHYROIDISM WITHOUT EXOPHTHALMOS

Query: "What would you prescribe for a girl of 14 who has hyperthyroidism without exophthalmos and with a normal heart action? She is, however, nervous and somewhat anemic."

Answer: How do you know that this girl has hyperthyroidism? She may have what is called "sympatheticotonia" or one of the symptoms of hyperthyroidism without actual thyroid irritability. This can be quite definitely determined by the use of the Thyroid Function Test, which is referred to elsewhere. The estimation of the B. M. R. (basal metabolic rate) will confirm this. If there is indeed a thyroid irritability, every effort should be made to remove foci of infection and other causes of the irritation, and *Pancreas Co.* (*Harrower*), a formula based upon the work of Dr. André Crotti of Columbus, Ohio, is advised. This formula is No. 6 on our list and the usual dose is one between meals and at bedtime.

I know of no better remedy for the anemia than *Hemoglobin Co.* (*Harrower*), which is given one or two doses three times a day. This is not really a hormone remedy but rather a form of organotherapeutic treatment based upon the fact that hemoglobin is the most easily absorbed and useful form of therapeutic iron that we know of. In this formula it is very nicely supplemented by nucleinic acid, which increases the white cell action, and spleen substance, which is accepted as a hemopoietic. Incidentally, you will find that it does not further accentuate the sympathetic irritability as is often the case with arsenic, etc.

6. ADRENAL SUPPORT DURING PREGNANCY

Query: "I have a case of chronic asthma who has been on your *Adreno-Spermin Co.* with marked improvement. This woman lately has become pregnant, and I am uncertain as to the use of this formula in such cases. She is still asthenic, her blood-pressure is now 110 systolic (it was considerably lower), and she has the fatigue syndrome to a marked degree."

Answer: In regard to the use of *Adreno-Spermin Co.* in pregnant women, I know of no detriment from the administration of a formula of this kind, more especially as, in this instance, the patient is quite asthenic and the blood pressure is still as low as 110. If she has a tendency to nausea and vomiting, which would be very probable with a detoxicating mechanism depleted as hers must be, No. 49 on our list, *Placenta Co.* (*Harrower*) would be indicated also to favor an earlier and more complete immunity to the placental proteins which it is believed may cause the anaphylaxis-like disturbances of early pregnancy; and which, incidentally may cause the hypoadrenal syndrome of which you write.

7. NAUSEA OF PREGNANCY A PROTEIN SENSITIZATION

Query: "Please give an explanation of your new method of controlling the nausea of pregnancy."

Answer: It is quite possible that the nausea and vomiting of pregnancy is a form of anaphylaxis or protein sensitization resulting from the absorption into the system of a new series of protein substances to which the body is not accustomed. It will be recalled that most women, during the first few weeks of pregnancy, suffer from this condition, usually in a minor manner, and that in the course of a short time the body becomes accustomed to handling these unusual substances and accommodates itself to these circumstances.

In some cases the character of these poisons is perhaps different from what it is in others, and certainly in some women there is a greater susceptibility to this poisoning. This is particularly true in individuals who are already unduly sensitive to proteins, and this includes women who may have had asthma or who have occasional periods of hay fever, or are susceptible to certain foods, such as straw-

berries, crab meat, eggs, etc. It is always of interest to discover, when investigating conditions in cases of vomiting of pregnancy, whether the individual has a tendency towards protein sensitization.

The idea of treating this condition by means of placenta organotherapy is based upon the fact that the body can accommodate itself to conditions that are brought about artificially, but are not really pathological. It will be recalled that the treatment of hydrophobia, for example, is the gradual administration of a poisonous substance to which the body becomes accustomed and immune in a shorter time than the bacterial developments can be consummated.

At all events, it is possible to favor the establishment of an immunity to the placenta proteins, and to my mind this is a basic reason for the successes that have followed the use of *Placenta Co.* (*Harrower*) in many cases of the severest types of vomiting and nausea of pregnancy. The idea is to administer a fairly generous amount of this formula (No. 49), for two or three weeks, and it has been found in many scores of cases—not in all of them, however—that within a week there begins to be a mitigating of the nausea and the vomiting and within two weeks, if there is going to be a cure at all, the result is complete.

I do not want it to be understood that I am advancing this as a panacea for the nausea of pregnancy, but I know that many cases have been under all sorts of treatment, including chloral by rectum, morphin hypodermically, the various synthetic sedatives, triple bromides, and entire rest in bed with special hygiene and diet, and were cured as by a miracle within ten days following the beginning of the placenta therapy.

The best method of dosage is to give ten grains three times a day for a week and then to increase the dose to fifteen or twenty grains three times a day. If the vomiting is quite continuous, it may be necessary to give this placenta preparation at a time and under circumstances when it can be retained, if necessary using sedatives to accomplish this. The idea is to get the absorption of this material into the blood and thereby bring about the immunity response.

8. THE DIAGNOSIS OF ENDOCRINE EPILEPSY

Query: "That I am interested in your products you already know from past correspondence, and my experience

with your *Antero-Pituitary Co.* in a number of cases of epilepsy prompts me to ask you this question: How can you determine in advance in which cases you may expect results from this treatment? Have you some way to find this out?

"You may be interested in the following recent experience: A man at the age of 28 began to have epilepsy which for ten years gradually became worse in spite of treatment by a number of physicians. He had gone through the usual bromide road and when I saw him a year ago at 39, he was having five to eight heavy *grand mal* attacks daily. For a year now he has been taking A. P. Co. After the first month the character of the attacks changed. After 2½ months my record reads 'a few *petit mal* attacks daily'. Occasionally he would have a complete attack. Now he goes six weeks or two months without any seizure. He is not cured yet, but he is certainly a different man."

Answer: Your experience was interesting, and the more so because of the age of the man and the number and severity of his attacks.

So far as I know there is no way definitely to determine in advance whether a given case of epilepsy is an endocrine one and likely to benefit from organotherapy, or not. Naturally if there are clear-cut signs of thyroid insufficiency or the appearance indicates a pituitary case, one would be justified in presuming that it might be an endocrine case. But even this does not give one the kind of impression that you are evidently seeking.

Suppose for one moment that a given case clearly has a thyroid-pituitary dystrophy. A half dozen or more indications may establish this to your satisfaction. This, however, is no therapeutic criterion. Merely because the case very clearly may involve the ductless glands does not prove that the endocrine trouble is at the bottom of the epilepsy, for all endocrine cases do not have epilepsy!

From what some like to call the "scientific aspect" of the subject I regret to say that it is not possible in advance to determine whether organotherapy is going to be of benefit in a given case of epilepsy or not. Yet, your own experiences have proved to your satisfaction that the use of my pluriglandular formula is indeed a worth while procedure, and I can quite understand that you must have had some failures you did not report. So have I!

As a matter of fact, while it is well to discover as many facts as possible about the endocrine side of a given case, this only favors the supposition that the case *may* respond

to the treatment of the endocrine feature, but does not by any means establish it in advance. Frankly, while I am being surprised continually by the reports like yours that I hear, of epileptics who have been treated successfully with *Antero-Pituitary Co.* (*Harrower*), I am equally discouraged about the very problem you bring up, for as far as I know, we are no further ahead today in determining the prospects from organotherapy and the prognosis of a case than we were before we began these clinical experiments. As things stand we know very positively that many epileptics, chiefly among the young as well as occasionally in older people, have been benefited by the use of this pluriglandular therapy. The attacks have been ended entirely or their frequency remarkably changed as in your case; attacks occurring from ten to twenty or more times a day being modified so that seizures occur once a week; or, again, very severe seizures have been changed in severity, i. e., *grand mal* has been lessened to *petit mal.* We know that with the changes in the epileptic aspects many times there has been benefit to other aspects as well, with a general increase in health and nutrition, resulting, undoubtedly, from the increased endocrine activities which we were attempting to modify in the hope that it might change the epileptic state. I know these results have occurred in many hundreds of cases, but our figures do not allow us to determine the relation between results and failures, and, of course of the latter there have been fully as many as the former.

As I see it, the frank answer to your inquiry is "There is no way to determine this in advance," but I must say that I shall never see an epileptic again without wanting to give him the benefit of the doubt and treating him from this standpoint, and if we fail after four or five months we have done no worse than ten thousand other doctors with bromides.

In closing it must be emphasized that organotherapy often is the means of determining whether a given case of epilepsy has a sufficiently important endocrine aspect to warrant this treatment. True enough, it is unscientific, unfortunately; but if we handle these patients right those who do not get results will not be so especially disappointed because we have warned them in advance of the limited prospects: whereas, those who do get results cannot find words to express their pleasure—and their opinions of their doctors!

9. THE ENDOCRINES IN MORPHIN ADDICTS

Query: "I am very much interested in morphin and drug addiction, and have come to the conclusion that in a well-established addict, the glandular secretions are diminished to a great extent and that the terrible withdrawal symptoms are caused by an antitoxin, which poisons the patient, the toxin—the morphin—not being there to counteract the antitoxin. Now I am wondering if these withdrawal symptoms could not be mitigated by the administration of some endocrine product. I should very much like to have your opinion in the matter."

Answer: As I have repeatedly stated, all poisons either stimulate or deplete the endocrine glands. The morphinist is always a case of hypocrinism, and the desolate picture that we so often see is sufficient proof of this. The elimination is tremendously low, the muscular tonicity is lessened, constipation, of course, is the rule, the urinary wastes are reduced two and sometimes three hundred per cent., the cardiac muscle is tired out, and the blood-pressure is practically always low. In fact, hypoadrenia is the proper name for the most usual endocrine symptom-complex of the drug addict.

I am not at all sure that the above suggestions about the "antitoxin" are correct. Of course it may be that the body has prepared a special substance to neutralize the morphin and that the removal of the morphin permits an excessive degree of toxemia by the very substance that was intended to neutralize the poisons which the body was anticipating. Be that as it may, the removal of morphin from a patient always leaves him tremendously depleted, and while the withdrawal is being carried on in the manner suggested by Dr. Ernest S. Bishop, of New York City, it is perfectly proper, and scientific, too, to encourage the depleted glands of internal secretion. I know of a great many cases of drug addiction who have been treated coincidentally with *Adreno-Spermin Co.* (*Harrower*) as a means of stimulating cellular activity, increasing the general muscular tone and raising the blood-pressure. This antagonist to adrenal insufficiency offers a service to the organism that cannot be secured in any other way. It is perfectly true, if the patient survives the serious conditions which accompany the removal of the morphin and, in some ways, can be permitted to reëstablish some degree of normalcy in his general cellular functions, that the glands of internal secretion

may, in course of time, reëstablish themselves fairly satisfactorily; but how much better it is to encourage them when in their greatest need, rather than to let them work out their own salvation.

The use of *Adreno-Spermin Co.* is indicated whenever there is cellular laziness and the fatigue syndrome. It supports the adrenal glands and thereby increases the cellular chemistry and the elimination of wastes. It also stimulates unstriped muscle, increases the cardiac power and raises the blood-pressure, and, besides this, the influence upon the alimentary musculature is always an advantage in cases of the type mentioned where constipation is the rule.

I do not want it understood that this is the treatment of the withdrawal symptoms of drug addicts; but that it is an adjuvant of extreme value and fundamental reasonableness is a fact that cannot be gainsaid.

10. EFFICIENT THERAPY IN MENORRHAGIA

Query: "I have two cases of severe metrorrhagia that have been treated locally and also with horse serum, calcium chloride, stypticin and other measures. Is there not something in organotherapy for cases of this type? Examination shows that neither of these cases has any apparent organic reason for the heavy flow."

Answer: If it is indeed true that both of these women have metrorrhagia or menorrhagia, with no organic cause, as those that follow a miscarriage or accompany fibroids, I believe that the functional condition is more likely to be modified by organotherapy than by all the styptic drugs that we have been in the habit of using. Cotarnin hydrochloride is certainly a styptic, but it only has a temporary effect, just as morphin has upon him, and is an opium derivative, by the way, while organotherapy tends very decidedly to remove causes.

In cases of this kind, since you have already operated and tried other measures without much success, surely organotherapy should be given a trial, and I recommend *Mamma-Pituitary Co.* (*Harrower*) for three reasons: First, mammary extract antagonizes ovarian hyperactivity and the pelvic congestion dependent thereon. It is a physiologic pelvic and uterine depletant, and many articles in the literature emphasize this anti-ovarian influence. Total pituitary substance tends to increase uterine tone and opposes the bogginess and excessive vascularity of the pelvis, such

as one expects in cases of this type. And further, it is combined with mammary substance, with very decided advantage, and many times I have proved that mammary therapy alone is not as efficient as a combination of mammary and pituitary.

You will note from our literature that this formula also contains a small dose of Bonjean's ergotin, for the following reason: Ergotin is known to be a uterotonic remedy, and has been successfully used many times in menorrhagia. The dose, however, is not sufficient to serve as a styptic, *but it sensitizes the uterus and renders it more responsive to the organotherapy* given simultaneously, and many clinical experiences show that its addition makes the other two associated remedies more efficient.

This formula has been used in many cases with success, and I trust you may have excellent results in both cases.

There is an ideal method of administering this formula: When the flow ceases (this may not be, but ordinarily there is a period of cessation of the flow), omit the remedy entirely for from three to ten days, depending upon the severity of conditions. During the next period of a week or ten days give one, three times a day at meals. During the week prior to the flow, *and through the complete flow,* give two, three times a day. Continue this treatment for at least three menstrual experiences, or preferably for a minimum of three months. It may be necessary to prolong it still more. You realize that one cannot state figures definitely where the flow varies so much, both in amount and time. Some flow very heavily for a week or ten days, and then are free for two weeks or so; while others flow for four or five days, at intervals of a week; and still others have a dribbling, insignificant flow virtually all the time. These different manifestations of menorrhagia make it impossible to set a hard and fast plan for the administration of this remedy. The point is to omit it when there is no flow or likelihood of it and to push it prior to the beginning of the flow *and completely through it.*

11. PROSTATIC HYPERTROPHY

Query: "Is the prostate a gland of internal secretion, and are there any chances with organotherapy in prostatic hypertrophy?"

Answer: Yes, it is now accepted as such by many. Based upon the not unreasonable theory that prostatic hypertro-

phy so common in elderly men may be due to a compensatory activity of this gland brought about as Nature's attempt to supplement the hypocrinism so usual at this age and especially the expected waning endocrine function of the gonads, an attempt was made experimentally to apply this idea in treating a number of cases. The results have been good, and while it is admitted that there are several fundamental classes of prostatic hypertrophy (as those due to a latent infection or to a new growth) which should not be expected to respond to this measure, there are pretty good chances of getting some satisfactory results from using *Leydig Cell Co.* (*Harrower*). The dose is one, four times a day, later increased, if it seems advisable, to two, three times a day.

12. THYROID ENLARGEMENT IN GIRLS

Query: "From time to time I have a number consulting me about glandular enlargement of the neck. They are usually in the late teens or early twenties, and I am wondering if it is connected with ovarian dysfunction."

Answer: The thyroid gland is very definitely related to ovarian function. Often the ovarian hormonic activities are not normal and the thyroid gland has a heavier burden to perform, which occasionally causes an increase in its size. This is one of the reasons for the quite common enlargement of the thyroid in girls at puberty. It will be recalled that the thyroid gland often enlarges in the early part of pregnancy, and this may be due to two causes: First, the effort of the thyroid gland to reëstablish a function which it presumes has become insufficient from some abnormal reason when in reality the temporary ovarian insuffiency of pregnancy is normal. Second, the thyroid gland is an important part of the detoxicating mechanism of the body, and there is naturally an increase in the toxemia during pregnancy, and the thyroid gland has to enlarge itself to accomplish the added work that it is called upon to do.

There is still another form of enlargement of the thyroid which is not so definitely connected with the age or sex of the patient, and which, of course, is due to poisoning or toxemia. In these cases the enlargement of the neck is due to irritation of the gland, and the condition is an entirely different one from the former.

In the thyroid enlargement of ovarian origin, thyroid extract is useful, but combinations of thyroid and ovarian

extracts are very much more useful merely because the enlargement is a manifestation of a pluriglandular function rather than connected solely with a disturbance of the gland itself.

My Thyroid Function Test, which is very easily applied, will enable one to differentiate between conditions of thyroid apathy and thyroid sensitiveness, and if there is thyroid apathy it is very easy to connect it with ovarian dysfunction by the clinical findings and symptoms and to treat the symptom-complex from a pluriglandular standpoint as, for example, with *Thyro-Ovarian Co.* (*Harrower*).

The most important point to bear in mind in regard to thyroid disorders in girls is the compensatory relationship between the endocrine glands. If this is remembered, the pluriglandular aspects of these cases will be more prominent and better appreciated, and the chances for a satisfactory outcome are multiplied many times.

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13. FAILURES WITH ADRENAL SUPPORT

Query: "I have used your *Adreno-Spermin Co.* in perhaps thirty cases, and have come to depend on it as a fine tonic in what you call 'the run-down cases.' During the past few weeks I have encountered two cases, one a man, and the other a woman, both around the fifty mark, who did not respond in the expected manner. In fact, so far as I could see, it did no good whatever, and I was much disappointed. Can you tell me the reason for this?"

Answer: I am glad you have had enough experience with this formula to have been convinced that it is indeed effective. If you had run across these unsatisfactory cases at first, you might have been tempted to question this whole method. But you have found out that there is decided merit for supporting the adrenal system; and that through these glands it is possible to increase oxidation, stimulate the circulatory apparatus, raise lowered blood-pressure and increase the "pep."

If you will read "Failures With Organotherapy," in my book, "PRACTICAL ORGANOTHERAPY," you will find several good reasons for occasional failures. The first thought that comes to me concerns the cause of the difficulty you have been treating—might it not be that the cause still remains, and that the continued adrenal depletion is more than the advantage that any adrenal support may accomplish? Again, in my experience, the greatest source of failure from the

organotherapy of chronic, intractable cases is the indeterminate responsiveness of the endocrine glands it is desired to encourage. In many cases the removal of toxemia, etc., and the use of *Adreno-Spermin Co.* (*Harrower*) for a couple of weeks or more, reëstablishes adrenal function and all is fine. If, however, the adrenals are fagged out and are unable to respond to the gentle encouragement thus offered, it is clear that the results will not be especially good, or at least not as rapid as in a more responsive case. Here, indeed, is the great difficulty in all forms of organotherapy. We depend almost entirely upon the reactivity of the glands it is intended to stimulate. If they are not capable of accepting these stimuli, or their powers of picking up the waiting hormones in the blood are reduced, it is clear that the results cannot be so quick nor so good.

Fortunately you are already converted; but had you not been by perhaps 28 good experiences, I can readily see how easy it would be for you to say—"More bunk. This man, Harrower, is claiming too much for his stuff—as usual!" As a matter of fact, this is not "bunk," nor am I a bit too enthusiastic about the immense possibilities of adrenal support in a large class of cases.

Don't forget that occasionally other forms of treatment, known to be effective hundreds of times before, have failed altogether, much to our chagrin. We expect this occasionally from our formulas, and if you can make your success-ratio 28 to 2 or approximately 93 per cent, you ought to be as pleased as I would be myself.

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14. ENDOCRINE ASPECTS OF COLD HANDS AND FEET

Query: "Will you kindly clarify a few of the statements which I have run across in your articles relative to the diagnosis and organotherapeutic treatment in high blood-pressure and hypoadrenia in particular?

"In your brochure on Adrenal Support, you remark that cold hands and feet are symptomatic of the asthenia of hypoadrenia, and, per contra, in your interesting article, 'Hypothyroidism, Infiltration and Hypertension,' published in a recent issue of the New York *Medical Record* (Nov. 20, 1920), you likewise credit cold hands and feet as being symptoms of that affection also. The first condition you ascribe to the poor circulation attendant upon low blood-pressure, etc., and the other to ischemia of those particular parts, resulting from pressure on the precapillary areas of

those parts by infiltrated cells surrounding those areas, both of which ideas seem to me to be pathologically correct.

"Accordingly, cold hands and feet are symptoms both of low and of high blood-pressure, which means that they are not pathognomonic of either state. Now, if a patient should call at my office, complaining of cold hands and feet, I would have to think of both conditions—high and low tension—and infer from other attendant symptoms which of the two conditions I have on hand. Therefore, this particular symptom will not materially aid me in the diagnosis of that case.

"You stated at the same time that thyroid extract is frequently indicated in cases of hypertension. If so, and thyroid is given to those cases in your formula, for example, *Thyro-Pancreas Co. with Spermin,* and you also suggest thyroid in the treatment of low blood-pressure and asthenia, which preparation likewise is also incorporated in your preparation, *Adreno-Spermin Co.,* and which is used for an entirely different thing, accordingly, I should judge that thyroid gland is beneficial in both high and low blood-pressure states. How do you reconcile these facts?"

Answer: You are a very careful reader of what I write, and so I shall attempt to give careful attention to your query, because I see that it is not an attempt to "bawl me out," nor is it an attempt to offer criticism for my making two statements, which seem to be entirely opposite, but is a frank effort to call my attention to seeming discrepancies and to acquire further information, which you may be able to use. I recall that you have written me before along similar lines, and have asked questions, which have illuminated both of our therapeutic paths, and therefore, I am very glad to go into this matter much more fully than I otherwise might do.

To begin with, there is no denying the fact that in asthenia with low blood-pressure, poor elimination, and, particularly, adrenal insufficiency, there is a tendency to circulatory stasis and, consequently, cold hands and feet. This is always found in adrenal insufficiency, where the circulatory aspects of the case are at all marked. You will recall that these patients very often have a subnormal temperature as well. You will find this particular symptom in various degrees of adrenal insufficiency. The post-influenzal hypoadrenia, which has been such a terrible burden upon the profession following the epidemic of a few years ago, is very commonly associated with a complex

syndrome in which circulatory inequality and cold hands and feet are common. This, I believe to be due to hypoadrenia. As you will shortly see, however, it is not necessarily solely due to this.

In my article published in the *Medical Record,* I called attention to a fact which I had not previously seen in the literature, viz., the principle relating hypothyroidism with high blood-pressure when there is a marked cellular infiltration resulting from the hypothyroidism. You have very accurately stated this in few words, when you say, "The other is due to ischemia of those parts resulting from pressure on the precapillary areas of those parts by infiltrated cells surrounding those areas, both of which [conditions] seem to me to be pathologically correct." Now it is also equally true, when thyroid insufficiency causes cellular laziness, and this in turn causes the infiltration which is pathognomonic of myxedema or of the minor forms of thyroid insufficiency, *that this infiltration would impede the capillary circulation,* and it does so absolutely; consequently in hypothyroidism there is a circulatory complex which causes cold hands and feet and, of course, this is the rule, for this is one of the typical findings in hypothyroidism, and not merely are the extremities cold, but the whole body is cold, the patient is cold, and the circulation is impeded very materially. As a matter of fact, this aspect of such cases is sometimes the first thing which calls our attention to the inactivity of the thyroid.

Hence, it is perfectly true that while hypoadrenia may cause cold hands and feet; so does hypothyroidism. And, Doctor, hypocrinism is the rule and this is a pluriglandular endocrine insufficiency in which the thyroid and the adrenals certainly are related and probably other glands with them. In other words, when you have a hypoadrenia you usually have hypothyroidism, and when you have hypothyroidism it is the most natural thing in the world for the inactive chemistry to bring about a condition of toxemia, which depletes the adrenal glands and consequently causes hypoadrenia. This means that cold hands and feet are typical findings in cases of either hypoadrenia or hypothyroidism, or both together.

Now for your well-meant criticism about the apparent discrepancy between the recommendations in the treatment of these cases. Thyroid is included in the *Thyro-Pancreas Co. with Spermin,* because of its value as a means of stimulating cellular chemistry, reducing the infiltration which

may be present, and thereby permitting, mechanically at least, as well as in other ways, I believe, an increase in chemistry and circulation. Thyroid is recommended as a remedy for high blood-pressure for another reason, viz., it favors detoxication and therefore lessens the very factors which are believed to irritate the pressor mechanism.

Thyroid is also found in *Adreno-Spermin Co.* (*Harrower*) which is used in hypoadrenia with low blood-pressure, poor elimination of wastes and especially urea, and the marked asthenic and neurasthenic conditions so common in chronic cases, and is included in this remedy because, as we have seen, hypoadrenia so commonly involves the thyroid and the two insufficiencies go together. When a person is all played out as a result of some toxemia or other condition, he requires not merely adrenal support, but an encouragement to the cellular chemistry which, as you know, is presided over by the thyroid, and consequently small doses of thyroid are equally valuable as an adjuvant to adrenal substance and other similar remedies for the treatment of hypoadrenia and run-down conditions generally.

Your deduction that thyroid may be beneficial in both high and low blood-pressure is correct, *and it is when there is a hypothyroidism underlying it.* Thyroid alone is more likely to reduce high blood-pressure, which is due to this infiltration, because of the mechanical influence already referred to. On the other hand, thyroid alone may raise blood pressure provided conditions are such that the encouragement of oxidation removes or lessens toxemia, which in turn releases the adrenal glands and permits them to regain a certain amount of their normal function and therefore increase the efficacy of the circulatory mechanism and, consequently, the blood pressure. As a matter of fact, thyroid extract is not given for its benefit in hypertension or in hypotension, but rather for its influence upon the endocrine glands, which are responsive to these factors and which may be connected with either the one or the other of these conditions.

In a previous communication I have referred to "the condiment influence of thyroid gland." This is another reason why it is included in these formulas, because, for some reason or another, a pluriglandular formula which contains a small amount of thyroid is very much more efficient therapeutically than where no such addition is made.

I do not know whether I may have reconciled these facts

to your satisfaction, but I do know this, that clinically the use of thyroid in suitable cases will increase the chemistry of the body sufficiently to reduce infiltration, which may be due to myxedema, or *myxedème fruste,* or to a minor hypothyroidism. It will also increase oxidation and reduce those factors which irritate (and later deplete) the adrenal glands; and where these indications are clear, the indicated organotherapy is useful, no matter whether the results seem to be opposite to one another or not.

I am glad to be able to subjoin here a part of the answer to this interesting correspondence:

"Your favor, enclosing the manuscript embodying the questions I propounded to you, and your answers to same, is before me. Your explanation elucidating the influences that both hypoadrenia and hypothyroidism exert upon the causation of 'cold hands and feet' is exceedingly clear and convincing, and the best explanation you or anybody else has advanced so far. I fully concur with your views.

"Your reasons for incorporating thyroid extract in your *Thyro-Pancreas Co.* on account of its influence in reducing cellular infiltration in (Barker's) precapillary areas and thereby reducing blood pressure, likewise its combination with adrenal substance (in your *Adreno-Spermin Co.*) for its influence in increasing oxidation and thereby promoting the eliminaton of toxins, and giving the adrenals a much-needed rest, and thus raising lowered blood-pressure, which you correctly ascribe to hypoadrenia, are also transcendently plausible and convincing. This leaves no doubt in my mind as to why thyroid is efficacious in both high and low blood-pressure states."

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15. DYSCRINISM AND DEMINERALIZATION

Query: "Is endocrine dysfunction due to mineral deficiency, or is the mineral deficiency due to improper functioning of the ductless glands?"

Answer: Very briefly, the answer to this important question is that endocrine dysfunction favors mineral deficiency because of the slowed and disturbed chemistry resulting from the lessened hormone stimuli which are necessary to maintain metabolism at its proper rate. The wastes which are not fully oxidized are many of them of an acid nature and tend to neutralize the body's reserve of alkaline salts and bring about the condition which the French have called demineralization. Just as soon as there is a deficiency

in this alkaline mineral reserve a further improper functioning of the ductless glands is favored. In some instances they may be irritated by these poisons, but in most cases their function is lessened—they are overburdened. It is difficult to determine just when cause becomes effect, and *vice versa;* but an insufficient activity of the endocrine glands and demineralization, or a lessening of the body's reserve of alkaline salts, are intimately related to one another, and from a clinical standpoint, should be considered simultaneously.

16. ORGANOTHERAPY FOR CANCER

Query: Please send me literature and other information on your remedy for cancer."

Answer: We have no remedy for cancer. I am not aware that organotherapy can be of any particular value in the treatment of cancer, though, of course, it is possible and, for that matter, very probable that patients with cancer have, accompanying the actual cancerous growth, a disturbed function of the glands of internal secretion which, with certain limitations, may respond to organotherapy.

For example: I know a case of carcinoma of the uterus in whom there was a very serious and foul-smelling discharge from the vagina. This was controlled entirely by means of *Mamma-Pituitary Co.* (*Harrower*), a formula which we ordinarily use for the treatment of menorrhagia and as a pelvic depletant. I had some difficulty in convincing the doctor that this was not going to make any noticeable difference in the actual cancer and, of course, I do not suppose it did, although I have lost track of the case. The fact remains that organotherapy was efficacious in an encouraging way in this instance.

Practically every case of cancer is "cachectic." Cachexia is nothing in the world but a toxemic malnutrition and one cannot have a condition of this kind without a serious depletion of the glands of internal secretion. Cancerous patients are invariably asthenic. They have very poor elimination. They are usually suffering from a typical syndrome of adrenal insufficiency, and, consequently, are in need of treatment of the character that we call adrenal support, and which is discussed quite fully elsewhere. However, this is not treatment for the cancer, but rather for the serious endocrine depletion which results from the toxemia accompanying the cancer.

17. ABDOMINAL PAIN FOLLOWING OVARIAN THERAPY

Query: "In two cases of dysovarism—as to the diagnosis of which I feel quite positive—there has been quite a little pain in the lower abdomen and slight nausea following the administration of the Thyro-Ovarian formula. I should be pleased to hear from you with any suggestion at your earliest convenience."

Answer: Ovarian therapy, as we all know, is useful for its homo-stimulant effect; that is to say, it encourages the functional activity of the ovaries in the same way that thyroid extract encourages thyroid activity and adrenal substance encourages adrenal activity. One of the uniform findings following the administration of a glandular extract for this homo-stimulative influence is an increased circulation and sometimes even an hypertrophy. It will be recalled that in his "law" Professor L. Hallion, of Paris, makes the following remark (note especially the part that is in italics):

"Extracts of an organ exert upon the same organ an exciting influence which lasts for a longer or shorter time. *When an organ is insufficient, it is conceivable that this influence augments its action, and, when it is injured that it favors its restoration.*"

I have had many clinical experiences which indicated to me that there was an increased circulation and functional activity of the ovary following a suitable period of ovarian organotherapy, and it is this increased circulation or physiological congestion which is likely to be the cause of the pain. The pain, I believe, may be due to the fact that the ovary itself is structurally disturbed or deranged *and that its capsule has become thickened and sclerotic* so that any engorgement or enlargement ever so slight, stretches this thickened and elastic covering, thus causing pain. Naturally we have an organic condition to deal with here, and while there is undoubtedly a functional one in these ovarian cases, organotherapy does not soften the sclerotic ovarian capsule nor does it make it more elastic. This engorgement is necessary to increase the function of the inactive glands; and in these cases evidently we really have two distinct evils to contend with.

As a matter of fact, when we find an ovarian dysfunction of an organic type with a sclerotic capsule, ovarian cysts or other organic changes in or around the ovary, sur-

gery is about all we can do, provided we cannot modify the function by means of suitable organotherapy. I have run across experiences of this type several times, in two of which an operation was performed and the presumed condition was found to be really present, and the ovary was "decapsulated" with considerable benefit.

Fortunately this does not occur very often, but I trust that it is a reasonable explanation of the condition that you find and that you may have very few cases like this in the future.

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18. MENTAL DETERIORATION FOLLOWING A FRIGHT

Query: "Have you had any experience in your therapy with mental deterioration following severe fright or shock? I have a little fellow of six, who is claimed to have been perfectly normal up to the age of four, talking, walking, etc. At that time he received a severe fright, and consequent nervous shock, which is said to be the cause of his suddenly losing his speech and gradually deteriorating. He is a very nervous, reckless child, with poor comprehension and concentration. What would you suggest along your line?"

Answer: Not having had a case of this type I referred this query to my friend, Dr. E. Bosworth McCready, of Pittsburgh, whose work with developmentally defective children is of a very high order, and he wrote me as follows:

"It has been my good fortune to see a number of cases presenting a history somewhat similar to the one you mention. Some of these were cases of congenital lues, in which the fright for some unknown reason seemed to cause to develop what practically amounted to a psychosis; others showed a markedly increased intracranial pressure, and on cranial decompression signs of hemorrhage or a mild meningo-encephalitis. One case, not due to mental stress, but to a convulsion following the ingestion of egg in a sensitized child, also showed evidence of hemorrhage on operation. All of my cases have showed a 'splitting off' of personality, and I can conceive of the same thing happening in an anemic, hypoplastic child without the occurrence of an actual organic lesion, though I do not believe this often happens. Organotherapy helps after the cause has been removed or counteracted; but is almost useless before."

If organotherapy is attempted in such a case, I would suggest the usual pluriglandular formula for hypoplastic and backward children—*Antero-Pituitary Co.* (*Harrower*) —and so far as I can see, no harm can come from applying this whilst further study and other treatment (for the suggested lues or local intracranial condition) is going on.

19. DISCREPANCIES IN PLURIGLANDULAR THERAPY

Query: "Cannon, in his work on the autonomic nervous system, has divided it into three parts: 1. Cranial, 2. Thoracic Lumbar, 3. Sacral. Nos. 1 and 3 make up what is commonly known as the 'vagus,' while No. 2 is known as the 'sympathetic' and the effect of stimulation of one is exactly opposed to that of the other.

"In the Department of Experimental Therapeutics of Cornell Medical College (see *Medical Record*, Oct. 16, 1920) it has been demonstrated that the thyroid is a 'vagus stimulator' and that the adrenals are 'sympathetic stimulators.' So far as some of your formulas are concerned it seems to me like giving an acid and an alkali together. If both these sets of nerves need toning up, it strikes me that it would be better to alternate either doses or days in the week.

"In view of the research work quoted I think this formula neutralizes itself more or less."

Answer: The work quoted above, and sponsored by Cannon and other investigators, is based upon splendid experimental studies and good reasoning. This position is accepted by practically all of the medical profession, and I believe that it is correct.

At the Mayo Clinic some work recently has been done indicating that the thyroid encourages the vagus, and the experimental work done at Cornell mentioned above emphasizes this. It is well known that the adrenal glands stimulate the sympathetic. However, I am not willing to admit that the administration of thyroid and adrenal substance is akin to "giving an acid and an alkali together." They do not neutralize one another and their function is extended very much further than their incidental influence upon the various divisions of the autonomic nervous system.

I admit that it seems like a discrepancy to offer an individual a vagus stimulator in conjunction with a sympathetic stimulator; but what about the content of the normal

blood which reaches these various organs or parts of organs? Does not this contain all the hormones and the various other chemical substances in solution or suspension? Does not the same drop of blood which happens to be passing through a given part of the body contain just as many anti-hormones as hormones, or vagus stimulators as sympathetic stimulators?

The great point, as I see it, is fully explained in the theory or hypothesis which I enunciated some years ago, (see "A Hypothesis of Hormone Hunger"—N. Y. *Medical Record,* 1919, xcvi, 276). This idea is based upon good reasoning although I do not think it can be proved scientifically. The facts are that the blood which goes to a given organ contains all these various substances in it, and the organ that is to be influenced exerts a wonderfully wise and subtle selective capacity, and my contention is that not merely is this true, but that *the selective capacity is modified by the need of that given organ* for the hormone stimuli. In other words, the greater the need, the greater avidity with which these substances are snatched from the blood as it passes by.

Now to come back to the possibility that pluriglandular therapy of the type mentioned "neutralizes itself more or less." In an individual who has the symptom-complex which in our estimation calls for stimulation by means of thyroid as well as through the adrenal glands, the hypothyroidism has brought about a certain combination of conditions which will be benefited only by giving the system the thyroid that it needs so much; and the asthenic syndrome in which hypoadrenia predominates requires adrenal support just exactly as the other condition requires thyroid support. It is surely well known that these two conditions fit in together and that hypoadrenia is very common in conjunction with hypothyroidism, and vice versa. Clinical experience establishes this, and the best proof of the reasonableness of the attitude which I have been emphasizing for many years is the clinical advantage rather than the theoretical reasonableness.

I think that it could be established theoretically that hypothyroidism and hypoadrenia naturally should go together, and that the administration of a pluriglandular formula directed at both of these together certainly renders a much broader service than to attack the one or the other singly. If at the same time the vagus is stimulated by one part of the formula and the sympathetic by another

part of the formula, the degree of these respective stimuli depends entirely upon the body's receptivity of these substances, and not upon our own will. As a matter of fact, *our will to render service to a patient is dependent entirely upon this endocrine receptivity,* and this is one of the chief factors in determining how valuable organotherapy is going to be in a given case—the responsiveness of these organs is the fundamental factor in determining its usefulness.

I am convinced, no matter whether certain substances stimulate the vagus and others stimulate the sympathetic, that when given together the general tone imparted to both the vagus and the sympathetic is an advantage as well as the resultant encouragement of the associated glands as a whole.

In so far as the suggestion to give these various differing preparations a part of the time and alternating them is concerned, I do not think this is good advice because if indeed the body has selective capacity enough to determine its needs along these lines, then this is present and useful during each of the two differing times, i. e., during the time that we are giving the one formula and the alternating time during which we might be giving the other.

This correspondent's suggestion may seem to bring up a discrepancy in the fundamentals of pluriglandular therapy, but too much water has passed under the bridge and too many experiences have established the reasonableness of considering pluriglandular conditions, and particularly hypothyroidism and hypoadrenia together, to make me want to change my attitude just because of some seeming *theoretical* disagreement.

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20. AN ENDOCRINE ASPECT OF PELLAGRA

Question: "I am asking for information regarding a case of pellagra. The patient complains of lack of concentration, is easily irritated, and the mental condition is very sluggish. There should be some possibilities of organotherapy in a case like this, should there not?"

Answer: So far as I know there is nothing in organotherapy that can definitely interfere with the pellagra itself. That is to say, the causative condition is not amenable to endocrine treatment, but it is very clear from all that I have heard and read about pellagra (and, by the way, quite a number of physicians have been kind enough to express their opinions about the use of our products in the treatment

of pellagra), that undoubtedly there is an endocrine aspect to this infection, just as there is to many other infections.

Your patient complains of lack of concentration, a sluggish mental condition, and the emotional aspects of the case show an irritability. Every one of these conditions is closely related to the sympathetic nervous system, to the endocrine glands, and to the detoxicating mechanism of the body.

Organotherapy directed at such conditions is likely to be of benefit, but you can readily understand that it will not reach the underlying difficulty. The pellagra must be treated in the accepted manner, and where the evidences of an endocrine imbalance are also present, as they are in many cases, then organotherapeutic interference would be worth while.

To my way of thinking, one of the best things that could be done in an individual of this type, would be to give a Thyroid Function Test first. Do not forget that the symptoms mentioned in your inquiry are also the symptoms of hypothyroidism. If this patient also has a low blood-pressure, a very limited circulatory tone, subnormal temperature, and the elimination of urinary wastes is low, then there is also a probable adrenal aspect.

At all events, the use of adrenal supportive treatment, as represented by *Adreno-Spermin Co.* (*Harrower*), certainly can do no harm in pellagra, and while I do not want it to be presumed that I am recommending this as a treatment of pellagra, I can confidently recommend it as a valuable remedy in conjunction with other measures and for the purpose of modifying the endocrine aspects mentioned.

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21. SYPHILIS AND DEFECTIVE CHILDREN

Question: "Answering your recent letter about the child I wrote you about, I wish to say that both Wassermann and Noguchi tests were positive, which speaks for syphilis. Let me know if you think that this syphilis might be the cause of the hypothyroidism and developmental difficulty. Should he receive the salvarsan treatment before giving the *Antero-Pituitary Co.* (*Harrower*), which was sent me? His mother shows a negative Wassermann. Should I have a Wassermann made of his father also? Does salvarsan cure cases of congenital syphilis?"

Answer: My personal experience indicates that syphilis is a common cause of developmental dystrophies in children. It is also one of the common causes of serious endocrine dis-

orders of the pituitary and other glands. Just as we expect lues to influence any part of the body and consider it as a serious toxemia, so we expect syphilis to be a common cause of dyscrinism, and we also expect the toxemia of syphilis to have a similar influence upon the endocrine glands to the toxemia of any other poisoning or infection.

The accepted anti-syphilitic treatment is not directed at the endocrine aspects of a case of syphilis with endocrine dysfunction, but merely at the cause of the difficulty. Certainly, in some cases, salvarsan and similar products bring about what are called "cures" of congenital syphilis, and accomplish wonders in some of these serious ductless glandular disturbances, the basis of which is a congenital or chronic syphilitic condition. This does not take the place of the organotherapy, because the removal of the cause of this dyscrinism merely allows the ductless glands to recuperate as best they may, whereas organotherapy by the principle of homo-stimulation encourages these glands to a better physiology and development, and replaces in part some of the substances missing as a result of the toxic influence upon the endocrine activity.

In the case of developmentally defective children found to be syphilitic the organotherapy may accompany the anti-syphilitic treatment, and *vice versa,* and I have repeatedly been brought in touch with patients who are developmentally deficient, and who have taken months of a presumably suitable organotherapy without the complete results that were hoped for and who did not respond to the treatment as they should have done *until the syphilitic aspect was uncovered and treated as well.* In other words, organotherapy has failed to accomplish all that was expected of it, because of a latent syphilis which naturally could not be influenced by the organotherapy alone. On the other hand, many a dystrophy of syphilitic origin is expected to right itself automatically when a series of anti-syphilitic treatments is given; and this is hardly fair, because it is expecting too much of the recuperative powers of the body. Hence, the proper thing to do in these cases is to determine as much as possible in regard to both the cause and effects of the underlying difficulty in these cases, and to treat the cause (the syphilis) and antagonize the effects as best we can (by organotherapy).

The child in question will be much better off with both anti-syphilitic and endocrine treatment. They supplement one another, as indicated, and experience with many cases

confirms the impression that there are certainly two sides to these questions; moreover many a failure has been due to ignoring one of them.

In regard to the invariable value or infallibility of the Wassermann test, I cannot say. Presumably it is a useful indicator as in the case of this child, and certainly a Wassermann should be made in the case of the father, especially as the mother is said to be negative.

In closing these remarks I cannot but emphasize *the necessity for considering the whole aspect of these cases,* not merely the obvious troubles before us but the underlying causes, and then when we have acquired all the information possible, treating all of the various phases of the case simultaneously, and in this particular instance, give the child the benefit of anti-syphilitic treatment as well as a treatment calculated to encourage the inefficient endocrines.

22. SYMPATHETICOTONUS IN HYPERTHYROIDISM

Question: "I have a young lady who was operated ten months ago for toxic exophthalmic goiter. The right lobe of the thyroid was removed. Considering her condition at the time of operation she made a good recovery. (Her symptoms were: marked exophthalmos, tremor so bad that she could not walk without aid, severe asthenia, and a pulse ranging from 160 to 190.) Since the operation her symptoms have cleared up considerably. There is a slight enlargement of the remaining lobe of the thyroid and the pulse is still 120. The tremor, however, is gone and there has been an increase in strength and weight. What do you suggest in pluriglandular therapy?"

Answer: Without a doubt the operation was necessary and the patient had a toxic goitre. However, these operations do not always remove the difficulties entirely, and, unfortunately, too many patients are left with very seriously unbalanced sympathetic systems. I really think that this patient has sympathetic irritability to a marked degree, evidenced by the fact that the pulse is still 120. (Parenthetically, let me call your attention to the first issue of *Harrower's Monographs on the Internal Secretions,* which gives you 120 pages of practical information on Hyperthyroidism).

Now the organotherapy that I have recommended for conditions of this kind is not so much directed at the actual thyroid enlargement as it is given for its influence upon the

endocrine system as a whole and, in turn, upon the sympathetic system. Personally I feel that in a good many of the cases where the thyroid is removed, the operation should have been directed at the tonsils, the sinuses, the appendix, or at least some focus of infection which was causing the serious thyroid irritability.

At all events, in addition to your further search for information of this type, I suggest that you follow the outline made in my little reprint, "My Routine in Hyperthyroidism." That is to say, in addition to removing the various emotional and fatigue factors, and emphasizing the value of rest, give her the sympathetic sedative formula, *Pancreas Co.* (*Harrower*), one, four times a day and perhaps, a little later, even two, three times a day, and combine with this the remineralizing, neutralizing formula, *Calcium Phosphorus Co.* (*Harrower*), of which she can properly take three one-gram tablets, crushed, with a generous drink of water, an hour before food, twice a day for three weeks, and thereafter on alternate weeks during the treatment.

Do not forget that organotherapy in hyperthyroidism is directed at the results of the hyperthyroidism rather than at the thyroid itself and the cause of its unusual activity.

23. THE ASTHENIC, THIN, BUT WIRY TYPE

Question: "You remember that a few weeks ago I asked you to discuss more fully the pharmacology and therapeutics of *Adreno-Spermin Co.* I wish you would take up especially the rationality of giving thyroid in cases of my type. Most of my doctor friends believe that thin, wiry individuals like myself do not put on weight because of a condition of hyperthyroidism and that they cannot see why *Adreno-Spermin Co.* is indicated in such individuals.

"What do you suggest for underweight cases who, despite plenty of food, do not put on weight because of excessive mental activity or overwork? With several months' rest very likely they would increase their body weight by 15 pounds or so, but they cannot afford it. This applies to quite a number of men that I know personally."

Answer: First of all, it is admitted that *Adreno-Spermin Co.* (*Harrower*) is a means of stimulating endocrine activity, cellular activity and the chemistry of the body in general. The large majority of individuals who are asthenic and run-down are suffering from an accumulation of their own wastes, and the adrenal depletion merely aggravates

this condition. Individuals with low blood-pressure, poor elimination of urea and subnormal temperature ordinarily have a pluriglandular insufficiency. The adrenals may be affected more definitely than the other glands, but most of these cases also need a small dose of thyroid. Practically all of them, of course, are benefited by the dynamogenic influence of the extracts from the interstitial cells of Leydig, and in many hundreds of experiences—I might say thousands—the combination has been superior to one form of monoglandular therapy, or another.

Now, I think that undoubtedly there are individuals whose chemistry is deranged in such a way that they have malnutrition, low blood-pressure and general asthenia, and yet their sympathetic systems are more on edge and their chemistry is more rapid than those just outlined; as a result of which they do not retain so many of the intracellular elements which make up the bodily wastes. Consequently, the degree of toxemia and asthenia is not so severe in this type, as you know.

You ask what change in the organotherapy I would recommend for a case like your own and those of your type. I do not know. Perhaps organotherapy is not the thing at all, and yet on the other hand I feel confident that your own experiences as well as those that you have seen in other cases indicate that the *Adreno-Spermin Co.* is the most efficient remedy for the ordinary run-down asthenic type of cases.

Now, we have two other preparations on our list that are of this type but that act in a slightly different way. *Hepato-Splenic Co.* (No. 5) is a nutritional stimulant which acts through the spleen and the liver. A great many cases of malnutrition are in this condition because the liver is not functioning normally, and usually a part of their difficulties is of such a character as to direct attention to hepatic insufficiency.

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24. SEVERE ASTHENIA FOLLOWING NASAL AND SINUS INFECTION

Query: "Five years ago Mr. X had a turbinectomy and later a large amount of necrosed bone was removed. After several months a pronounced anemia developed, accompanied by lassitude which has persisted for a long time, causing an aggravated neurasthenia. Might this condition result from destruction of the pineal gland at the operation, or after it?

"Again, a young lady operated three years ago for infected ethmoids and turbinates later developed pronounced neurasthenia and an acute melancholia. There is still a persistent lassitude. It is believed that these two cases are similar and that the pineal may have been destroyed. Would the administration of the pineal gland either alone or in combination with adrenal and thyroid substance be of benefit?

Answer: I have never heard of a nasal or sinus condition involving the pineal gland. It might more likely be a possible source of infection reaching the pituitary gland. I do not think that the pineal gland is half as important a gland of internal secretion as some have indicated, and I have had very little to say about the value of pineal therapy because I do not think that there is much to it! Incidentally, it takes approximately 5,000 pineal glands to make a pound of the useful extract, and it is the most expensive of all the glandular products obtainable, and not half as valuable as we had hoped it might be. Further, it will be recalled that its chief prospective source of value was in certain developmental disturbances in children. The experiences of those connected with the institution at Vineland, N. J., which were very carefully worked out and published some years ago, seem to have convinced the medical profession that the pineal gland is not nearly so intimately connected with developmental disturbances in children as is the pituitary gland.

In these cases there may have been some condition of pituitary dysfunction, and this would be manifested by not merely the asthenia and other conditions mentioned above, but by a tendency to adiposity, a condition of lessened sexual activity, not merely functional, but organic, and an increase in the tolerance to sugar: in other words, the triad of symptoms that one expects to find in hypopituitarism. There might also be a condition of pituitary enlargement with pressure symptoms, including severe headaches. The diagnostics of pituitary dysfunction are fully discussed in another section.

In my estimation, the adrenal glands are the most likely to have been involved in cases of this kind. In fact, the infective conditions so commonly encountered by the nose and throat surgeon must all of them have a more or less important adrenal aspect; and I would like to say here that there are many nose and throat specialists who have come to the conclusion that in addition to removing as best they

can the foci of infection in the tonsils, sinuses, etc., *the simultaneous support of the adrenal glands is worth while treatment,* for it is a means of antagonizing the lassitude, asthenia, and consequent neurasthenia which so often accompany conditions of this kind.

Hypoadrenia very commonly accompanies infective conditions, and it makes no difference whether the infection is in the head, gall bladder, appendix, pelvis, or elsewhere. In these cases very often there is an associated thyroid insufficiency on the very general principle that the thyroid is concerned in the immunizing response and that an excessive demand upon its function is liable to play it out.

The treatment for this aspect of these cases, in my estimation, would be adrenal support such as is represented by the well-known *Adreno-Spermin Co.*

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25. DEFICIENT MAMMARY DEVELOPMENT

Query: "I have a friend who has a beautiful daughter of about 15, who seems normal in every way, except that her breasts are not develcping. Her mother's breasts never seemed to develop, though she nursed her baby normally. Do you know of anything which would promise benefit?"

Answer: Mammary therapy has been recommended by a number of French writers for the development of mammary form and function, though my own experience has been practically limited to the application of this idea as a galactagogue and not as a bust developer. It is remarkable how some very small-breasted women can nurse their children, and also how splendidly apparently atrophic or hypoplastic mammary glands can be encouraged to function by means of organotherapy.

We have a formula on our list, called *Mamma-Ovary Co.* (*Harrower*), which is used for the treatment of excessive menstruation in girls, and which might possibly be beneficial in the hypoplastic condition referred to. We have another formula called *Placento-Mammary Co.* (*Harrower*), which is used chiefly as a galactagogue, and, by the way, it is one of the most remarkably efficient of all the formulas on our list. Either of these two forms of pluriglandular therapy might be worthy of a trial, or a combination of thyroid and mammary without ovarian substance might be worth considering.

Of course, there is more to a condition of this kind than an endocrine or glandular aspect, and the use of mechanical

measures, especially cupping, is worthy of consideration, although I do not think that it should be recommended unless there is some very special need for the development.

I know of two cases that have followed the combined line that I have mentioned, *i. e.*, the use of *Mamma-Ovary Co.* and treatment by the electrical cupping apparatus, and also the generous application of cold mitten friction to the breasts (very carefully) with quite considerable development.

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26. CHRONIC BRONCHITIS

Query: "Have you had any success with glandular products in the treatment of chronic bronchitic conditions?"

Answer: Bronchitis, like any infection, has its general influence upon the body and, *vice versa,* the general condition of the body has everything to do with the establishment or control of a bronchitis. In other words, bronchitis is not merely a disturbance of bacterial origin involving the bronchial mucosa. The same thing is true of tuberculosis and also of asthma, both of which are closely allied to bronchitis as all know and are virtually always associated one with the other. In other words, tuberculosis is pretty nearly always a chronic bronchitis and too often its real seriousness is obscured by the use of this title; and asthma is very often nothing in the world but a chronic bronchitis with an unusual sensitiveness of the body to the protein products of the bronchial secretion and its contained myriads of bacteria.

To say that organotherapy constitutes the treatment for chronic bronchitis would not be fair. On the other hand, to say that organotherapy will cure chronic bronchitis would give offense to some. But the fact remains that when an individual has dyscrinism—usually the hypoadrenia syndrome which I have discussed so many times recently—the regulation of this dyscrinism, the increased circulatory efficiency, the bettered cellular chemistry and the general advantage to the patient have given them an especially added responsiveness to be able to overcome the bronchitis.

In this class of cases the usual treatment is directed at the chest, with ammonium chloride or other expectorants to change the character of the bronchial secretion, hydrotherapy to increase the local circulation, and tonics for their general value. The expectorants agree very nicely with the tonics and organotherapy, and so does hydrotherapy, hy-

giene, dietetics, etc.; but to my way of thinking, *Adreno-Spermin Co.* (*Harrower*) takes the place of and gives a much more satisfactory service than the usual tonic mixtures that we have been in the habit of using in these cases.

The principle of adrenal support has nothing to do with bronchitis as such save only as the endocrine glands have to do with the regulation of the body's defenses, an influence which has been quite thoroughly established these many years. To answer the question again and briefly: Organotherapy is a valuable adjuvant in the treatment of chronic bronchitis, caring as it does for conditions so commonly associated with bronchitis and so ordinarily left untreated.

THE VOMITING OF PREGNANCY

Query: "You may be interested to learn of an experience I had with a case of serious vomiting of pregnancy with your *Placenta Co.* Mrs. B, 3-para, previously had had 'terrible times' with nausea and vomiting in her two previous pregnancies; came under my care six or seven weeks pregnant with 'the same old trouble' and 'as bad or worse than ever.' I treated her with chloretone, triple bromides, and later morphin. Practically no results in a month. A friend of the lady told of having been given some 'glandular medicine' by a doctor in Salt Lake, which stopped her similar trouble very soon. I got this doctor's name and wrote him, was put in touch with your Denver office, and finally got the remedy for my patient. In ten days everything was lovely. Patient beginning to get up, holding everything down, and practically no more nausea, the vomiting having ended several days before.

"I would like to know why this measure is not better known? I have tried it already on three other cases and it was 'a sure shot.' Have you any more literature on this subject?"

Answer: One reason why this preparation is not better known is that it consists largely of a product which is not accepted by "authority." You know that there are certain self-constituted arbiters of the destinies of therapeutics who sometimes are not as well posted on some things as some other people, and it happens that these individuals have ruled that this and several other organotherapeutic products are not proper for good physicians to use. (See Section I, under the heading, "The Character of These Products.")

Another reason why the preparation is not better known is that there are limitations to my work. You may not know it, but a few physicians feel that the work of The Harrower Laboratory is altogether too commercial. Just yesterday I received a letter from a physician in Texas, calling me down and closing his letter in the following terms: "I believe the majority of people—at least a large percentage of all professions—are gullible, and I resent any suggestion that I exploit or be exploited. I cannot see any motive except a desire for material gain in such extensive advertising as you now carry out." He forgot that our dealings are solely with the medical profession, and that success only comes to those who "keep everlastingly at it."

There are many good things known to certain physicians and commonly used by them which are not always appreciated by their colleagues. I am glad to say that there have been many instances of the type outlined in your letter. I recall one, but this time the preparation was *Placento-Mammary Co.* (*Harrower*), a galactagogue formula. At a meeting of the California State Medical Association a prominent physician came up to me, pulled a capsule out of his pocket and said: "Could you tell me what this is?" I told him that it was not always easy to determine the character of a glandular preparation by mere observation and asked him what it was supposed to be for. He said that one of his patients having had difficulty in nursing her children had learned from one of her friends that in similar circumstances she had been given a certain preparation which helped very materially to increase the amount of her milk, and kindly divided her supply with the other patient. It began to render service almost immediately and when this woman who had been visiting came back to Los Angeles and visited her physician, she told him of the experience and he got one of the capsules, which was the one shown to me. This man had every chance in the world to know of my work. And yet it was through a coincidence similar to your own that he was brought in touch with the galactagogue value of this particular product. Like *Placenta Co.* (*Harrower*) the galactagogue preparation is "not accepted"—it is in advance of the field.

I was very much interested in the fact that already you had duplicated your experiences several times and that you believe that this particular method of treating the vomiting of pregnancy is "a sure shot." It is not, because it is very clear from the clinical experiences which have been related

to me and some of my own as well, that this form of organotherapy only reaches a certain type of cases of vomiting of pregnancy. As I have tried to explain elsewhere, evidently this particular class of cases includes the women who, having a tendency to protein sensitization, are particularly disturbed by the protein evidently produced in the placenta and carried into the circulation. In other words, they have an anaphylaxis against these products, and if you will investigate a number of cases of vomiting of pregnancy, you will find that many of them will report to you that they cannot eat certain foods—strawberries, shell fish, eggs, etc.—because they usually disagree with them, and cause a rash, nausea or other unpleasant reactions.

The administration of the *Placenta Co.* seems to increase the immunity of the body somewhat in the manner that we can increase an immunity to hydrophobia after the bite and before the organism has time to develop its full and fatal influence. Whether this explanation of its value is correct or not it does indeed have value. For instance, a doctor writes: "I have now brought another woman to the middle of pregnancy with practically no nausea except for a few times when she was not taking No. 49—*Placenta Co.* (*Harrower*) for a short time. She had dreaded this pregnancy very much because of her extreme nausea with her last baby, and she and her husband both wished a termination of the pregnancy because of her past experience. She is now going about at five months with no symptoms and has practically stopped treatment."

If you have a patient with nausea or vomiting of pregnancy, no matter how early during the pregnancy or how serious it may be, certain it is that the use of *Placenta Co.* (*Harrower*) is a reasonable measure, because it has helped before, as you know very well. Perhaps this is one of the empirical procedures that I am criticized for, but if you succeed in helping your patient, what do you care for all the criticisms of those who have nothing whatever to do with your personal affairs? The patient takes care of you and shouts your praises from one end of the town to the other, and in addition to the professional advantages that this may have, you certainly have a good deal of personal satisfaction in having accomplished something that otherwise you might have failed to do. As Elbert Hubbard once said, "There is a sweet satisfaction in having passed along a good thing"—and *Placenta Co.* (*Harrower*) *is a good thing in the vomiting of pregnancy in many instances.*

28. DEFICIENT NUTRITION IN A CHILD

Query: "I have a three year old child weighing only 18 pounds, who is very much below par in every way. Mentally, however, the child is as bright as one could expect and it occurred to me that instead of the *Antero-Pituitary Co.* which I have used successfully in defective children, some other preparation would be more suitable. Can you give me some help?"

Answer: Ordinarily *Antero-Pituitary Co.* (*Harrower*) is given to children who do not develop properly in so far as both their growth and mentality are concerned. The child you write of apparently has not grown in stature, although mentally it is normal and may be diminutive or perhaps the case is merely one of insufficient nutrition. If the child's height in relation to its age is not far from the average and the appearance indicates malnutrition, another line of treatment suggests itself.

The first thing to find out is whether there is some removable cause of the difficulty, as, for example, worms. It is also necessary to find out if the child's nutrition is low because of a digestive incapacity, i. e., a lack of assimilative power on the part of the bowel. This is sometimes found out by dietetic experiment and fecal analysis which should be carried out for sometime in conjunction with every effort to reduce alimentary toxemia and lessen the burden upon the organs that are affected by such toxemia.

The use of the bacillus Bulgaricus, as in the culture known out here in California as "Vitalait", is sometimes very efficient in the treatment of such children and, in addition to this the newer vitamine therapy that is now coming into vogue certainly helps to facilitate the nutritive powers in this class of cases.

One of the best morphogenic nutrition-stimulating remedies is phosphorus, and it happens that three of the best and most acceptable forms of phosphorus are of animal origin—lecithin is the chief of these and the other two, nucleinic acid and the glycerophosphates, while originally secured from animal glands, now are made more cheaply from other sources.

According to Potter, phosphorus in small doses stimulates metabolism and especially the growth of bones. The effect on metabolism is to increase the nitrogenous product and to diminish the excretion of carbon dioxide. Phosphorus is used chiefly to promote nutrition. It is also useful in nerv-

ous exhaustion due to overwork as well as in rickets and osteomalacia. Potter suggests certain phosphorus preparations as a gastric tonic to be given to weak, anemic children with the view of improving the appetite and nutrition.

We have a preparation of phosphorus, known as *Nucleo-Lecithin Co.* (*Harrower*), No. 14 on our list, the administration of which sometimes has exerted a very remarkable stimulating effect upon nutrition, particularly in the young. This contains a generous dose of 90-95% lecithin, supplemented by suitable amounts of nucleinic acid, for its known cell-stimulating and especially white-cell-stimulating effect (nuclein is said to be one of the most useful leucocytogenic remedies) and calcium glycerophosphate as a useful "chemical food."

The use of this formula in children of the type mentioned sometimes gives just the fillip necessary to the nutritive exchanges, and the use of 15 to 30 grains a day, in divided doses, is to be recommended in conjunction with a careful dietetic handling and the eliminative regulation already mentioned.

Incidentally, this phosphorus preparation is sometimes very valuable in senile neurasthenic conditions, which are accompanied by malnutrition and cachexia.

29. ADRENAL INDIGESTION

Query: "I have a patient who evidently has hypoadrenia—the blood pressure is 90-55, temperature about 96.2 each morning, and she is tired and weak. For years her chief difficulty has been with her digestion. Food lies in her stomach and ferments. Her breath is very foul. She has abominable eructations and I have had to wash out her stomach several times. It occurs to me that besides rest, dietetic control and the hydriatic measures we use here, some of your treatment might help. Would you give the Adreno-Spermin formula or *Secretin Co.*, and why?"

Answer: We do not know whether the adrenal insufficiency to which you refer and which the woman undoubtedly has, is a cause of her digestive insufficiency, or the result of it. Either might be the case. The tiredness and weakness to which you refer undoubtedly extends to the alimentary musculature, and her digestive tract must be equally tired. She might have had some original difficulty, the nature of which would deplete the adrenals, which is really at the bottom of her indigestion—a focus of infec-

tion, a serious infectious disease, like influenza or a severe shock.

I am reminded of a translation which was made here of an article by Hernando, a Spanish physician whose article appeared in *Medicina Ibera,* Madrid, for October 11, 1919. This writer calls attention to the influence of the glands of internal secretion upon the digestive apparatus, not only by the hormones themselves, but through the intermediary of the vegetative nervous system. What Hernando calls "universal asthenia" and also ptosis of abdominal muscles and contents, are also probable consequences of changes of this character. There is no doubt also that the secretion of the gastric glands may be modified by endocrine function and this is usually in the line of hyposecretion. Hernando calls attention to the fact that persons with adrenal insufficiency have a defective gastric secretion. His own research and that of others, especially in France, has demonstrated that hypoadrenia provides conditions favorable for the development of gastric ulcer and the modified functioning of the vegetative nervous system favors a tendency towards low resistance to infection.

Emphasis is laid upon the injurious effects of fatigue and the emotions on persons with hyperchlorhydria and gastric ulcer and it is suggested that these conditions may be explained by the exhaustion of the adrenals which they induce. Attention is also called by this same writer to the benefit realized as the adrenals are permitted to recuperate under a rest cure or when adrenal therapy is advised. This article is supplemented by a very large bibliography and to my mind is strictly in harmony with the facts.

Taking it for granted that the hypoadrenia which you determine is present should be treated, the natural question arises whether *Adreno-Spermin Co.* (*Harrower*) should be used, or *Secretin Co.* (*Harrower*), and I would be willing to give either to this patient with the expectation of some benefit. The former has a more general effect. That is to say, it acts upon the glands which are involved in the complex. *Secretin Co.,* on the other hand, contains a sufficiently generous dosage of adrenal substance to get a good deal of the tonic effect from it, especially upon the alimentary muscles and in addition has a large enough dose of bile salts to encourage the liver which must be equally inactive with the rest of the digestive system and finally, most important of all, the duodenal principle, secretin, which I really believe has a therapeutic value especially in the very class of cases

of which this woman is a type.

I would continue to wash out her stomach and certainly she will be advantaged by the sanitarium treatment that she is able to get there. In addition to this I would give *Secretin Co.* (*Harrower*) ten grains, three or even four times a day, preferably between meals.

Another important aspect to these cases is the matter of remineralization to which your attention already has been called. I would give her *Calcium-Phosphorus Co.* (*Harrower*) three tablets, crushed, with much water, and as far away from food as possible, twice a day for at least a month in attempt to antagonize the tendency to acidosis unquestionably present in so asthenic and toxic a person.

30. PARKINSON'S DISEASE

Query: "What is your opinion in regard to the parathyroid treatment of paralysis agitans?"

Answer: That it is of some prospective benefit in certain cases; but that it is not an encouraging method of treatment. Paralysis agitans still is an incurable disease. It certainly seems to involve the parathyroid glands as Berkeley of New York and others have found. I have recommended *Parathyroid Co.* (*Harrower*)—a combination of active parathyroid extract, spermin from the interstitial cells of Leydig for its general tonic effect, and bile salts for the hepatobiliary stimulating effect, with reported benefit in several hundred cases of paralysis agitans. The drooling has been ended in many instances, the insomnia is often benefited quite early in the treatment, the tremor has been lessened, and I know of cases where the patient, previously unable to feed himself and to button his clothes, after two months of treatment had recovered these faculties.

W. N. Berkeley believes that "sixty to seventy per cent. of those who give this a fair trial for three months, have been greatly benefited" and since the prospects in Parkinson's disease are so poor, they should at least have the benefit of the doubt and try the parathyroid therapy in conjunction with whatever measures seem advisable, as for example, hyoscin, massage and hydrotherapy.

31. EARLY POSTPARTUM MENSES

Query: "I have a woman age 33 now nursing her fourth baby, who reports that her menstruation is usually established from three to five weeks after delivery. She always

has had difficulty in nursing her children and each of the first three began to use the bottle within a month or six weeks of their birth. At present, the fourth baby is five weeks old and nursing already is quite unsatisfactory. The baby has a digestive difficulty and the mother fears the bottle. A slight menstruation began a few days ago. Uterus is still large, boggy and quite tender. Have you any organotherapeutic suggestion?"

Answer: My suggestion is to use *Placento-Mammary Co. (Harrower)*, ten grains, three or four times a day for two weeks and perhaps thereafter in one half the above dosage. This form of organotherapy is not merely galactagogue in its influence, as has been proved in a good many thousand cases, but it exerts a decongestive influence on the pelvis. It has been known actually to prevent early postpartum menstruation. I recall meeting a physician in the lobby of the office building in which I used to be and she told me of some experiences that she was having with a nursing mother. She asked me the question if I did not believe that No. 3 (the formula we are talking about) had some influence on the uterus as well as on nursing, and I naturally told her it must have, because nursing has an influence upon the uterus. Subinvolution is quite common in women who do not nurse their children, and it is believed by those who have studied the matter that one of the reasons for ovarian and uterine troubles in women, is the fact that they so often neglect to nurse their children and get the reflex benefit that the use of this function has upon the pelvic organs.

This doctor reported that the treatment had not merely encouraged the production of milk, but had depleted the pelvic organs, lessened the size of the uterus and stopped the flow—for there was no menstruation until seven months, whereas previously two or three months had been the usual time that menstruation began. Maybe it was a coincidence, but it has happened a good many times.

[I am able to add here that the suggestion made to this correspondent caused considerable improvement in the amount and quality of milk. The baby gained very nicely, continued nursing for five months longer, the involution of the uterus was noticeably hastened and instead of a menstruation which ordinarily began three to five weeks after delivery and, mind you, *had followed this plan for three previous experiences,* now the menses were not reëstablished until seven months, which we believe is clinical proof that this phase of organotherapy is really effective and that

it serves (1) as a galactagogue, (2) as a uterine involutant, (3) delays abnormally early postpartum menses and (4) increases the baby's weight and health.—H. R. H.]

By the way, a Pasadena physician was in the office yesterday telling some wonderful things about this formula. A case in point was a woman, two months overdue, with a 12½-pound baby, 48 hours in labor with a tear clear through into the rectum. Naturally she had a hard time afterwards, nursing was not very successful and "the uterus was clear up to the liver several days after." The *Placento-Mammary Co.* was given with immediate and progressive benefit both to the subinvoluted uterus and to the nursing.

32. SYMPATHETICOTONUS AND TUBERCULOSIS

Query: "I have been in the habit of using your *Adreno-Spermin Co.* as a tonic in patients with tuberculosis and must confess that it has seemed to be of great advantage. I now have a case of tuberculosis to whom I fear to give thyroid in any dosage and will be pleased to have your suggestions regarding another formula for the same purpose as No. 1 but without any possibility of irritating an already overirritated thyroid."

Answer: All conditions of glandular depletion, to my way of thinking, are the result of glandular stimulation, and your patient at present has a toxemia which is irritating various parts of the organism, including the thyroid.

Doubtless the depletability, if I may use the word, of various glands differs in degree and some thyroids, especially, take the toxic stimuli very seriously, and a condition of hyperthyroidism complicates the original trouble. *Adreno-Spermin Co.* (*Harrower*) contains one twelfth of a grain of desiccated thyroid in each dose. Enough, perhaps, to be a detriment to an individual with a well-defined hyperthyroidism, but not enough to cause any harm if used for a short time. We have another formula, however, *Pancreas Co.* (*Harrower*) which, as you know, is used in the treatment of the heart hurry, sympathetic irritability and other difficulties of hyperthyroidism. Why not consider that your patient has sympatheticotonus, as undoubtedly he has, *and treat it?* In a case of this type *Pancreas Co.* will have its usual benefit upon digestion, which is always advisable in tuberculosis, it may exert its expected sympathetic sedative influence and. best of all, it has been used by at least three physicians, with whom I am personally acquainted, in tuber-

culosis with a mild hyperthyroidism with benefit to both conditions.

I am glad to know that you have acquired confidence in the use of *Adreno-Spermin Co.* (*Harrower*) in the asthenic, run-down, tuberculous individuals. It is worth while treatment, and so is the *Pancreas Co.* in the particular variation of these cases that you refer to.

33. POST-ENCEPHALITIS SEQUELAE

Query: "Have you secured any results in the treatment of post-encephalitis cases? I have an 18-year-old girl who was quite well up to November 1919 when she had epidemic encephalitis. Since that time she has shown a steady failure. At times her appearance indicates a typical dementia praecox with blank features, excessive salivation, but mentality not especially disturbed. Then again she presents a Parkinsonian aspect with tremor and a rather festinating gait. Her blood pressure is low (105-60). Is there any possibility of a serious glandular disturbance with some hope from organotherapy, or must I throw her into the discard, as will naturally be the case if her trouble is due to definite organic lesion in the stem and cord?"—Washington.

Answer: It seems to be generally believed that encephalitis-lethargica, or as the British have come to call it, "sleepy sickness," is in some way related to the same fundamental causative element (an organism, it is presumed) as influenza. I am sure that this may be true and that the epidemic of sleepy sickness which has been a good deal worse abroad than in this country, is nothing but a specialized recurrence of influenza.

Without a doubt there are serious changes in the cerebrospinal structures. The paralyses and the conditions that you outline so lucidly in your question, are not, to my mind, functional, but rather the result of definite changes in the actual nerve structures.

It does seem a terrible thing to have to "throw her into the discard" as you indicate, and it has happened that some of these cases of epidemic influenzal encephalitis have been benefited in some ways by treating the endocrine aspects which naturally follow so serious a toxemia. The masses among the profession have accepted our belief that influenza causes hypoadrenia, and that the most serious manifestations of influenza are the changes in the adrenal structure,

or at least, adrenal function, which leave the patient so tremendously played out, asthenic, and unable to accomplish anything either cellularly or by use of the will.

Every case of serious toxemia, no matter whether bacterial or chemical, must have some sort of an adrenal aspect. The adrenal glands are involved in all of these cases, and I really believe that there is a very serious endocrine depletion involving not merely the adrenals *but all of the endocrine glands,* just as the whole body is seriously changed in its metabolic and cellular functions as a result either of the toxemia, or the combination of circumstances connected with the lethargic aspects of the case. In other words, *there is an endocrine lethargy also.*

In such a case, especially when the blood-pressure is low as here, I would advise adrenal support. I recommend it routinely in all cases of early or late influenza, in the simple, easy cases, or in the most serious and almost hopeless cases. It is good practice to encourage the adrenals or to prevent their depletion—routinely. I know of cases who are alive today as the result of adrenal support. I know of other cases whose entire aspects were changed within a week or two by adding to an apparently suitable line of treatment, the support of the adrenal glands by the use of the *Adreno-Spermin Co.* (*Harrower*) which we have shouted about these many years and which has been used successfully in literally thousands of cases of influenza.

I admit that it has not been used as frequently in epidemic lethargic encephalitis and I could not say in advance what the results might be in the girl to whom you refer, but if she were my patient, I would most assuredly give her the benefit of the doubt and support her adrenals generously for a period of three or four months *if only as a diagnostic measure.*

Give her the *Adreno-Spermin Co.*—a five-grain dose every three hours for a month and thereafter one, four times a day, at meals and bedtime. In a case like this the principles of remineralization which I have frequently referred to in my writings obviously apply. Antagonize the tendency to acidity so common in these cases, remineralize and lessen the burden of the already overworked endocrines. Give the *Calcium Phosphorus Co.* in doses of three grams, crushed, an hour before meals twice a day for three or four weeks and thereafter on alternate weeks.

Add these measures to all of the other measures that may occur to you from the standpoint of medicine, electrother-

apy, dietetics, or general hygiene. Organotherapy and remineralization are invariably adjuvant measures. I do not care whether the results are credited to the organotherapy or to other things which may be done simultaneously. The point is to do everything possible for these unfortunate individuals, and one of the possibilities is along the lines that I have spoken of. It may not be a very hopeful procedure, but to my way of thinking at least it is well worth a trial.

34. HYPERTENSION AT THE MENOPAUSE

Query: "I have two cases in women, one about 40 years old and the other 45, both of whom are in the change of life, whose blood-pressure ranges from 190 to 240. These women seem to have a similar condition and it occurred to me that you might be able to give some assistance."

Answer: Functional hypertension is a common symptom of the menopause. Chief among these disturbances of this period are irregularities in the circulation and sympathetic nervous system. The removal of the ovarian hormone, to which the body has been accustomed for perhaps 30 years, permits compensatory irregularities on the part of the other glands, notably the adrenals, and many times the hot flushes and the circulatory imbalance are related to a considerable increase in the systolic blood-pressure.

The subject has been given consideration elsewhere (see Section V, Chapter 15) and to make a long story short, there is indeed an organotherapeutic measure that can be given with prospects of results in these cases. It consists of a small dose of *thyroid*—a remedy known to have a depressor effect in certain functional high blood-pressures for reasons which are discussed in my paper "Hypothyroidism, Infiltration and Hypertension" (*Medical Record*, Nov. 20, 1920); *pancreas* for its equally useful depressor influence which is believed to be brought about in two ways—the one by its antagonism to adrenal irritability and the other by its lessening toxic conditions in the alimentary canal—and finally, *ovarian substance* with corpus luteum.

This combination, known as *Thyro-Pancreas Co. with Ovary* (*Harrower*) (No. 30 on our list) may be given with the expectation of lessening not merely the high blood-pressure but some of the associated circulatory difficulties so common at this period. The dose is five grains, four times a day, and in certain instances after a short period of treatment the amount may be doubled for a month and there-

after when some control has been noted, one five-grain dose three or four times a day will suffice to continue the treatment for a total of at least three months.

I know of really spectacular reductions in blood-pressure as a result of this treatment. A case comes to mind of a woman who, like your own cases, was in the change of life, whose blood-pressure was 260 and she was not standing it very well because with it she had terrible headaches which were very disconcerting. It was brought down exactly 100 points in three months and the last record that I had was 160-90.

35. THE TONSILS AND THE THYROID

Query: "Does the removal of the tonsils aid in the treatment of an enlarged thyroid? Give treatment."

Answer: Very often the tonsils are responsible for thyroid enlargement, and whenever a case of goitre comes to the office and one finds that the tonsils are enlarged and infected or that there is an inactive infection and the deepened crypts contain purulent material, in my estimation, the tonsils should be removed.

Without any question, the absorption of poisons from the infected tonsillar tissue stimulates the thyroid and is a factor in the condition about which you ask. There are many reports in the literature emphasizing the necessity for caring for infected tonsils in connection with goitre and, especially, hyperthyroidism. (See the first issue of *Harrower's Monographs on the Internal Secretions* and especially the chapter on "Focal Infection" in the section on diagnosis in this publication.)

It is well to assure oneself of the character of the thyroid enlargement, and this can be done very frequently by the local examination coupled with my Thyroid Function Test. If we have a case of thyroid irritability, I have already outlined the treatment quite fully in the article entitled, "My Routine in Hyperthyroidism." (See also Section V, Chapter 10.) On the other hand, if it is simple goitre of the common variety and involves a deficiency in the service of the thyroid of the body, then my best suggestion is to use iodex ointment externally, a piece about the size of a Lima bean, rubbed upon both sides of the neck every night and No. 18 on our list, *Iodized Thyroid Co.* (*Harrower*) of which the dose usually is one, four times a day. This formula contains iodid of

iron, desiccated thyroid and nucleinic acid (nuclein) and is an excellent remedy for simple goitre.

If by any chance the thyroid is enlarged because of an ovarian dysfunction—and this is quite common—of course it will be necessary to take care of this simultaneously.

36. SOME POINTS ON ENDOCRINE DOSAGE

Query: "In looking over the dose table in the Appendix to your book, "Practical Organotherapy," I note a wide discrepancy in the dosage of various substances. Comparing the dose table with statements in the various formulae and other places in the body of the book there seems to be quite a little difference. Just one instance: In *Gonad Compound* the dose of pituitary gland (anterior lobe) is given as 1 Gr. (see page 93), while the dose table gives the dose of this substance as 1/5 of a grain. The dose table also gives the dosage of thyroid as from 1/12 to ½ Gr., which is only a fractional dose compared to some recommendations."

Answer: I am sorry that there has been some misunderstanding to prompt your query, for if you will look at the table again you will see in the first column (average dose t. i. d.) that in line 25 "pituitary-anterior" is given as "1-5." That means *one to five grains per dose* three times a day and not one fifth of a grain as you indicate. If you will read up or down this column it could not have meant one fifth of a grain because the first item on the list, "Adrenal total," is ½-2 gr., and the last, "Trypsin," 1-5 gr.

In regard to what it is claimed is a mistake about the dose of thyroid which, as you recall, is given as one twelfth to one half a grain: I admit that quite a number are in the habit of giving much larger doses of thyroid even of the desiccated gland, but I agree with them only under unusually exceptional circumstances. Possibly you have in mind a very excellent English preparation of thyroid, the dosage of which is based upon the *fresh gland* represented in each tabloid, and you will recall if you will look at my dose table that the relation of dry powder to the fresh gland in the case of Thyroid, (U. S. P.), is as one to six; that is to say, it takes six parts of the fresh substance to produce one of the dry, and naturally this makes a great deal of difference in the actual amount of thyroid principle that is given in the final desiccation. We follow the U. S. P. and all our products are dosed upon a basis of *desiccated substance* in each formula.

37. ICHTHYOSIS IN A BOY

Query: "I have a case with a scaly condition of the legs and a roughness of the skin on the forearms in a boy about seven years old. This has been called ichthyosis and he has had it most of his life. Which of your preparations would do the most good?"

Answer: Fortunately, true ichthyosis is not very common, but a roughened, thickened, scaly skin is not unusual in thyroid insufficiency, the more especially as it is a chronic condition of years standing in a child only seven years old.

In an interesting article by J. M. H. MacLeod of the Charing Cross Hospital, London, (*Practitioner,* London, Feb. 1915, p. 298), he writes under the subheading "Xeroderma and Ichthyosis," in the following words:

"A scaly developmental anomaly such as ichthyosis suggests itself as a suitable cutaneous disorder for thyroid medication, and the remedy has been employed in this connection with favorable results in a considerable number of recorded cases. The precise condition of the thyroid in ichthyosis has not been worked out definitely, and would appear from reports to be inconstant; but clinical examination of the thyroid, especially in young children, is almost invariably unsatisfactory, as the gland is difficult or impossible to detect by palpation. [Incidentally, the Thyroid Function Test had not come into use at that time.—H. R. H.] Winfield described a case of ichthyosis in a child who lived two and a half weeks, and at the autopsy the thyroid body was found to be absent. Colcott Fox reported a case of ichthyosis in a child of 16 months of age, which improved under the ingestion of thyroid extract, and in whom he was unable to detect any thyroid gland. . . . Up to the present it has not been definitely proved that the thyroid functioning is constantly defective in ichthyosis. . . .

"A number of observers, however, have found that definite benefit followed the ingestion of thyroid in certain cases of xeroderma and mild ichthyosis in children, and that when thyroid treatment is started a desquamation takes place, which is rapidly followed by an improvement, the skin becoming smoother and assuming a more healthy appearance. Unfortunately, the improvement usually ceases when the thyroid treatment is discontinued, and a relapse is liable to take place."

The Thyroid Function Test is quite a helpful means of determining the extent of the thyroid insufficiency, but it

is good practice to apply thyroid therapy without this test in a case of this type. On the general principle that thyroid deficiencies of years standing, especially in growing children, must needs have involved the associated glands, it is proper to consider them also in the treatment, and *Antero-Pituitary Co.* (*Harrower*), which contains in addition to a small dose of thyroid suitable amounts of the anterior pituitary substance and thymus, would be a reasonable measure.

For a boy of this type, give one dose three times a day with his food. At the end of a month if there have been no results, add to the same treatment of thyroid, ½ grain, one dose a day, as, for example, in our No. 9 *Thyroid Co.* (*Harrower*). At the end of the second month, provided the results are not complete, continue the same treatment but give two half-grain doses of thyroid daily.

38. ORGANOTHERAPY IN CHOREA

Query: "Can you give me some suggestions as to the treatment of chorea with glandular extracts?"

Answer: There are quite a number of references in the literature to a possible relationship between disturbed function of the endocrines and chorea. Quite a number of children with this motor difficulty have been found to show simultaneously evidences of glandular dysfunction, notably of the thyroid and parathyroid glands. Some Italian investigators have emphasized the relationship between tetany and the convulsive manifestations that are connected with hypoparathyroidism and chorea, and there are four or five papers in Italian medical literature speaking highly of parathyroid therapy as of prospective merit in the treatment of chorea, especially when it is combined with calcium salts (since parathyroid dystrophies usually are related to disturbances of the calcium metabolism).

From the standpoint of the thyroid gland the French have been most active in their study and several writers emphasize the importance of considering the thyroid aspect of every child with chorea, and, if there is evidence of dysthyroidism these writers naturally urge the control of this condition as well as the treatment of the chorea.

Personally, I do not think that chorea is essentially an endocrine disease. When it is found in conjunction with dyscrinism or disturbed function of one or more of the glands of internal secretion, naturally the treatment should

include measures directed at the endocrine trouble, or organotherapy.

In developmentally defective children in whom chorea is one of the manifestations, *Antero-Pituitary Co.* (*Harrower*) should be given. This may be supplemented by parathyroid if it is desirable and occasionally the results will be encouraging. Peculiarly enough, as your letter was on my desk for this reply a physician called in to consult me and in his conversation he told of a case of chorea in a child of eleven that was virtually cured entirely by this particular formula, and nothing else. This, of course, is not usual and I do not want you to feel that I am recommending this method of treatment for the chorea itself, but rather for the underlying dysfunction which is so often found in children who are not normal in regard to their endocrine development. Our *Parathyroid Co.* (*Harrower*) might be used experimentally in chorea in conjunction with the above.

As this goes to the printer I am in receipt of a letter from a physician in Missouri who had consulted me some months ago about a complicated case with chorea. It is an interesting report—and friendly:

"You may remember the case of the 14-year-old girl I wrote you about early in August. Well, I am proud to say, she is steadily improving and the parents, who formerly had lost all hope after years of trial in various cities under seemingly all pathies and forms of treatment, are now in the seventh heaven of delight at the rapid changes for the better in her condition. I am sending now for the third package of *Antero-Pituitary Co.*

"The choreic conditions are disappearing fast and she now walks perfectly erect and goes up and down stairs without assistance as well as you or I. Appetite, sleep, bowels and kidneys all good—speech is difficult yet and the ligaments of the left arm still are heavily contracted, but the general atrophy of the limbs and the facial expression are approaching rapidly to normal. Congratulations, *Mon ami!*"

39. LATENT TUBERCULOSIS

Query: "You state that 'the endocrines are involved in *every case* of tuberculosis'. Perhaps you are right. What about these glands in the early, latent cases? I should think that the best time to get after the glands is early. Give us some points about it."

Answer: The earlier the better. I am convinced that the earliest beginnings of the so-called "pre-tuberculosis stage" are connected with endocrine depletion. A severe illness, infected pair of tonsils or the proverbial "bad cold" *always involve these endocrine regulators.* It cannot well be otherwise. Some very frank and pointed consideration was given to this very subject by my friend, Dr. O. W. McMichael, of Chicago, in an article published in the New York *Medical Record* for February 21, 1910 (page 317). This is an unusually virile article and the author, well trained in the school of experience with these cases, hits straight from the shoulder in regard to poor diagnosis, faddism, and the really important factors which are involved in latent tuberculosis and commonly overlooked.

This reference to McMichael's excellent article is made in order to note the following unusually accurate word-picture of this condition: "The tired school girl is brought to us because she cannot keep up with her work. She is tired all of the time. She has not lost weight, she always was thin, just like her father, who always was thin and who, by the way, is carrying around in his chest an old tuberculous cavity that no one knows about, though they do say he was threatened with lung trouble when he was a young man. She has no cough so we do not look at her chest. We do notice that her thyroid is a little larger, but many girls at puberty have enlarged thyroids. She is just run down, so we prescribe a tonic, whatever that is. She picks up again, and in two or three years she is sent to a sanatorium. We do not see that that enlarged thyroid meant a response to a cry for help. We did not know that the blood was burdened with an excess of tubercle toxins, that the adrenal glands were unable to meet the burden of controlling elimination and telegraphed the pituitary body, which in turn whipped up the thyroid. Disturbance of endocrine balance is a result of toxemia. Tubercle toxemia is constantly present in varying degree in latent tuberculosis. Lowered blood pressure is a constant sign of tubercle toxemia."

The "cry for help" to which this author so aptly directs attention is extremely important, *and its importance is in direct proportion to the frequency with which this phase of tuberculosis is ignored.* Adrenal insufficiency is the most common endocrine disturbance in tuberculosis and is believed by many to be the direct cause of the low blood-pressure, the marked asthenia, the poor elimination of urinary solids, as well as the subnormal temperature. It is begin-

ning to be fairly well known by my readers that I am convinced that *Adreno-Spermin Co.* (*Harrower*) is an efficient means of antagonizing just this condition—but it does not cure the tuberculosis! It merely helps to take care of a very obvious deficiency which certainly ought to be taken care of in conjunction with other lines of treatment necessary to help these poor people.

40. SUBNORMAL TEMPERATURE

Query: "A number of my patients, especially those who have had tuberculosis and are in the arrested stage, have a noticeably reduced temperature. It varies from 92 (in an extreme case) to 97 and usually averages about 96. Is this related to the ductless glands and is there not some chance for organotherapy?"

Answer: A subnormal temperature is one of the expected findings in adrenal insufficiency. In many items that I have written, reference to the subnormal temperature is coupled with a poor elimination of urea in the 24-hour urine, a lessened systolic blood-pressure, marked asthenia, and malnutrition—in other words, everything is "below par". The same thing is true in cases of hypothyroidism and not merely is there an actual reduction in the production of heat but the patient feels very cold, the circulation is poor (impeded by the infiltration so common in these cases) and the temperature naturally is a degree or two below normal.

In neurasthenia, following severe infectious diseases and especially in the post-influenzal state, a subnormal temperature is very common and in most instances it will be found in conjunction with a thyro-adrenal insufficiency. In many instances the lowered temperature may be raised and there is a general increase in well-being and circulatory activity following the application of adrenal support in the manner which I have suggested many times.

In tuberculosis, particularly, hypoadrenia is common. This has been referred to in several articles from my pen (see Sec. V, Chap. 2, and Sec. VI, Chaps. 32 and 39.)

In cases with a sub-normal temperature, it is quite interesting to estimate the B. M. R. (basal metabolic rate). Many of these individuals have a basal metabolic rate which is 10, 20 or even 25 per cent below the normal. The reason for the lowered metabolism is identical with the reason for the lowered temperature—endocrine insufficiency; and whether it is purely of thyroid origin, as in certain cases, or a pluri-

glandular proposition, as I believe, does not change this particular finding.

I have on my desk the records in a case referred to me of a woman in the thirties whose weight was only 61 pounds with her clothes on! In the investigation which I initiated, her B. M. R. was -19.7 per cent, and her temperature was 96.2 Fahrenheit or at least two degrees below normal temperature. It happens that Du Bois and his associates recently have shown quite accurately that the B. M. R. is changed about seven points by each degree of reduction in body temperature. Therefore, in this case with the temperature two degrees below normal, one could expect at least a rate of -14, where in reality it was -19.

Very often these individuals with a subnormal temperature are not eating enough, and if they are studied from the standpoint of the calorific amount of food consumed, some interesting things may be developed.

In these cases the encouragement of the undoubtedly lagging endocrine glands, plus other methods calculated to increase oxidation, and the supplying of the needed heat producing foods, may make a very noticeable difference; and, by the way, in many instances of tuberculosis where the temperature was decidedly subnormal and where there was a considerable degree of asthenia, previous good treatment was made better by the application of the principle of adrenal support just mentioned.

SECTION VII

APPENDIX

1. A GLOSSARY OF TERMS

A number of terms which are not in general use necessarily insinuate themselves into a book of this character. Some of them are not found in the late dictionaries. Of course, the list cannot pretend to be complete, but at the suggestion of a number of readers of the first two editions this addition is made to the appendix in the hope that it may be especially helpful to many.

Activator. A substance which changes a ferment from an inactive to an active form. Ex.: HCl activates pepsinogen as secreted by peptic glands to pepsin.

Adrenalin. The trade name for the pressor principle of the adrenals, isolated by Takamine. The hydrochloride in 1 in 1,000 solution is used generally.

Adrenin. A short, euphonious, physiological term for the adrenal medullary principle, preferred by Cannon and other authorities to adrenalin and epinephrin (*q. v.*)

Alpha-Iodin. E. B. Kendall's first name for the essential thyroid principle. See *Thyroxin.*

Antihormone. A chalone or antagonistic hormone; name given first to the internal secretion of the pancreas, because of its action upon the adrenal or chromaffin hormone.

Asthenia. Lack of strength and vitality; the fatigue syndrome.

Autacoid. (Greek, self; a remedy). A generic term suggested by Sir E. A. Schäfer to include all the chemical messengers—i. e., hormones and chalones (*q. v.*)

Basal Metabolism. Energy metabolism determined calorimetrically from fourteen to eighteen hours after eating and when the individual is at complete rest.

B-iminazolylethylamine. A depressor and utero-stimulant amine prepared from histidine (and therefore also from intestinal extracts) by the action of putrefactive bacteria.

B. M. R. Abbreviation for "basal metabolic rate."

Cachexia. Malnutrition in cancer and other serious toxic diseases. (Found to be result of hypoadrenia.)

Chalone. (Greek, I relax). A term suggested by Sir E. A. Schäfer to indicate the hormones which do not excite—the antagonistic hormones. Ex.: the "Langerhansian hormone."

Chemasthenia. A term intended to refer to deficient metabolism "asthenic chemistry" as compared with myasthenia, neurasthenia, cardiasthenia, etc. See *endocrine asthenia.*

Chemical reflex. Another term for "humoral reflex" (*q. v.*)

Chromaffin. Staining with chromic acid or its salts. A term applied to the adrenal medulla and its hormone—i. e. the chromaffin hormone.

Coenzyme. A substance which manifests a coöperative activity between an enzyme and some other non-colloidal substance. Ex.: The influence of bile salts on pancreatic lipase. The process differs from activation, for the combination is dissociable instead of permanent. A coenzyme can be separated from an enzyme by dialysis.

Cretinism. Major hypothyroidism in children corresponds to the acquired myxedema in adults.

Demineralization. A condition in which there is a deficient mineral content of the blood and tissue juices; lessened alkaline reserve; acidemia; etc.

Dyscrinism. Disordered function of the endocrine glands as a whole. (Also called "dysendocrinism.")

Endocrine (Greek, within, internal; I separate, set apart). Pertaining to the internal secretions. Occasionally written "endocrinous". (Both words are philological monstrosities. In Greek a verb can be compounded directly only with a preposition.)

Endocrine Asthenia. An asthenic condition of the endocrine glands; also an asthenic condition brought about by hypocrinism including chemasthenia, myasthenia, neurasthenia, cardiasthenia, etc.

Endocrinosis. An endocrine neurosis.

Epinephrin. The term given by Abel to the active pressor principle of the adrenal gland. Used erroneously by some to indicate all adrenal preparations, irrespective of their origin.

Gonads. The essential sex glands—i. e., the testes and the ovaries.

Histotherapy (Greek, tissue). A term rarely used instead of opotherapy (*q. v.*)

Homostimulant. A term used to indicate the particular action which organic extracts and lipoids exert upon the organs to which they correspond.

Homostimulate. Self-stimulate, i. e., the stimulation of cells corresponding to those from which the homostimulant (*q. v.*) is secured.

Hormone. A chemical messenger, which, formed in one organ, travels in the blood-stream to the other organs of the body, and effects a correlation between the activities of the organ of origin and the organs on which they exert their specific effect. Ex.: secretin (in duodenum) activates the pancreatic cell and changes the inert pancreatic protrypsinogen to trypsinogen, ready for use as soon as it reaches the intestine (and in this case further activated by enterokinase).

Humoral reflex. The activity brought about through the blood and the hormone contents of its plasma (as compared with the nerve reflex).

Hyperendocrinism. The opposite of hypoendocrinism; not, however, clinically known. (Should be hyperendocrisia; see note on *Endocrine.*)

Hypocrinism. A short and more frequently used term for hypoendocrinism. (*q. v.*)

Hypoendocrinism. Deficient internal secretory activity; usually refers to pluriglandular insufficiencies, as special words (hypopituitarism, hypothyroidism, etc.) are applied to individual deficiencies.

Hypoplasia. In this book, particularly, a deficient growth and development.

Hyposphyxia. A syndrome described by Martinet in which there is a semi-asphyxia of the cells due to hypotension, venous stasis and circulatory inefficiency. Believed to be largely of adrenal origin.

Infundibulum. The posterior lobe of the pituitary body.

Interstitial gland. *See Leydig cells.*

Interrenals. The adrenal cortex (as opposed to the adrenal medulla.) In some fishes they are separate organs.

Leydig Cells. The essential internal secretory cells of the male gonads; the interstitial gland.

Myxedema. An acquired thyroid insufficiency of considerable degree; major hypothyroidism.

Myxedème fruste. Hertoghe's disease; a latent but well-defined form of hypothyroidism.

Neuro-circulatory Asthenia. A term originated during the war to indicate a syndrome which is believed to be due to endocrine asthenia. Usually found associated with hypocrinism.

Parhormone. Products of katabolism endowed with a physiological or hormone-like action (Gley). See *Ponogen.*

Pluriglandular. A term used to indicate a form of compound glandular therapy—i. e., the simultaneous administration of several extracts.

Polyglandular. A word of mixed derivation which should not be used. See *Pluriglandular.*

Ponogen. (Greek, work). A cellular waste which may serve as a "chemical messenger" to influence some remote organ (Laumonier). See *Parhormone.*

Prosecretin. The precursor of secretin, found in the duodenal walls and changed or activated to secretin by hydrolysis with action of HCl.

Remineralization. The treatment of demineralization (*q. v.*) by means of suitable alkaline tissue salts.

Secretin. The typical hormone from the duodenal mucosa secreted as prosecretin, and later activated by HCl. (1) Pancreatic secretin: the secretin which activates the pancreatic cells; not secretin from the pancreas. (2) Gastric secretin: the secretin which activates the gastric cells.

Sequardotherapy. A little-used term for opotherapy (*q. v.*), based on the name of the "discoverer of animal therapy"—Brown-Séquard.

Spermin. A definite chemical body obtained from the testicles, said to be a nerve tonic and cell stimulant (von Poehl, Petrograd).

Stimulin. A term sometimes wrongly used in the place of "hormone". Stimulins are, according to Metchnikoff, certain protective bodies in blood-serum, which produce immunity when inoculated by stimulating phagocytic action.

Tethelin. The active principle of the anterior lobe of the pituitary body isolated by T. Brailsford Robertson, of Berkeley.

Thyroxin. Trade name for alpha-iodin, the recently-discovered crystalline iodin containing active principle of the thyroid gland.

Vitamine. Evidently a plant hormone, e. g., the life-encouraging, nutrition-stimulating, growth-developing plant principle.

2. DOSE TABLE

Preparation	Aver. Dose t. i. d.	Rel. Dry to Fresh	Compar. Cost
Adrenal (total)	½-2 gr.	1:6	2
Adrenal Cortex	2-5	1:15½	9
Adrenal Medulla	3-10 m.	1:20M	1200
Amylopsin	2-10	1:8	1-5
Bile Salts	1-5	1:40	1
Bone Medulla	1-2 dr.	.....	3
Brain Substance	5	1:6	1
Corpus Luteum	2-5	1:5	10
Duodenal Scrapings	5-10	1:12	1
Hemoglobin	3-5	.....	2
Kidney	5-15	1:8	2
Lecithin	½-3	.....	3
Liver	5-15	1:6	1
Lung	10-20	1:10	1
Lymphatic	1-5	1:5	3
Mammary	3-10	1:4½	2
Nuclein	⅛-½	.....	3
Ovary (total)	2-5	1:6½	2
Pancreas (gld.)	2-10	1:5	1
Pancreatin	2-5	1:8	1-5
Parathyroid	1/50-1/20	1:5-5	60
Parotid	2-8	1:5	1
Pepsin	3-10	.....	2-5
Pineal	1/10-1/2	1:7	40
Pituitary (anterior)	1-5	1:5	7-5
Pituitary (total)	¼-1	1:4½	9
Pituitary (posterior)	1/10-1/2	1:4	15
Pituitary (post. prin.)	3-15 gt.	.....	800
Placenta	3-5	1:6½	3
Prostate	3-5	1:6	3
Spermin (Leydig cells)	2-3	1:9	5
Spleen	3-10	1:4½	1
Steapsin	2-5	.....	4
Submaxillary	2-5	1:8	3
Testes (orchid)	3-10	1:7½	1-5
Thromboplastin		.....	4
Thymus	3-5	1:6½	2
Thyroid	1/12-1/2	1:6	2-5
Tonsil	½-1	1:7	5
Trypsin	1-5		5

Note: For explanation of the above table see page 404.

Explanation. The dosage is in grains except where otherwise stated, and the amounts given are approximate. They may be repeated three or more times a day. The relation between a finished desiccation and the original fresh glandular parenchyma is stated as accurately as possible here, special attention is called to this as certain trade products are dosed on a basis of "fresh gland substance," obviously to the detriment of convenience and even safety. All the above doses are based upon finished products and follow the U. S. Pharmacopeia in the few instances where gland "extracts" are listed therein, and is based upon a factor called "1" which represents the cost of the less expensive desiccations such as spleen, liver, etc. Where an occasional product is not dry, as bone marrow, thromboplastin, "Liq. Hypophysis" (posterior principle of the pituitary) naturally no figures can be given in the fourth column.

3. THE "SANITABLET"

It happens that glandular desiccations are decidedly hygroscopic and if exposed to moisture darken in color, becoming malodorous and, from the standpoint of appearances, are spoiled. (So far as I know these physical changes do not destroy the therapeutically active principles.)

Gelatine capsules are also hygroscopic and a certain degree of humidity will cause them to "melt". As a result of these two factors we frequently have found ourselves in trouble, especially in certain climates, and I have spent a great deal of time and money in an attempt to overcome these difficulties. I am glad to be able to say that they have been overcome entirely.

The New Package. We now supply my pluriglandular formulas as *"Sanitablets"*—compressed, friable tablets, packed by the Sanitape machine leased from the Ivers-Lee Company of Newark, N. J. Each dose is individually wrapped and hermetically sealed in strips. They are put up in small cartons of 20 doses, 5 cartons to the package, or 100 Sanitablets in all. The word "Sanitablets" is original with me and is protected by registration in the U. S. Patent Office, November 22, 1921.

The Sanitablet is never touched, and the waxed wrapper makes it moisture-proof and air-tight. It is the best preventive of deterioration that can be imagined, and the ad-

vantages of this are particularly obvious in tropical, humid countries. I am assured, for instance, that supplies sent to India, reaching there and being used during the tremendously damp "monsoon season" were in perfect order—a thing which would be quite impossible with the gelatine capsules.

This package, which has been in use for nearly a year, also favors the dispensing of smaller amounts than 100 doses, if desired, without inconvenience or loss—since each unit of 20 Sanitablets is boxed separately. This package is also quite a convenience from the standpoint of the patient, since each dose may be detached without touching the Sanitablet, or several doses can be torn off and slipped into the pocket or purse and carried *sealed* until they are taken.

Prevents Unfair Competition. Still another great advantage lies in the fact that this package effectually prevents substitution. Unfortunately, many inferior substitutions have been palmed off for real *Harrower* products. It is easy to fill similar capsules and the temptation is strong and, unfortunately, many have succumbed to it with detriment to our own reputation because numerous letters indicate that these substitutes did not accomplish what has been expected from the original products.

For instance, a Denver physician who had been using our preparations for some years had several cases who seemed to be progressing nicely on the use of *Thyro-Ovarian Co.* (*Harrower*). As many physicians know, it is necessary to continue the use of this particular formula for several months and not infrequently a patient will use from three to four hundred doses. Within a week this physician heard from three of the patients that "the capsules do not seem to be the same as before and they are not doing as much good", or words to that effect. The coincidence prompted the physician to make an investigation. He secured some of the capsules presumed to be of our manufacture and when analyzed they were found to contain a generous quantity of an excipient not used by The Harrower Laboratory—indicating without a doubt that a substitution had been made. If this physician had not been thoroughly converted to the value of these preparatons and thus a friend of our work and of organotherapy, he might have come to the conclusion that we were dishonest in not adhering to my original, effective formulas. Indeed, it was with this in mind that he corresponded with us.

To illustrate this further, I recall a recent communication from South America referring to a certain lady who had been using No. 6, *Pancreas Co.* (*Harrower*) with very considerable improvement over a period of several months. The supply was low and diminished until it was necessary to go without the preparaton for seven or eight weeks, because of the fact that our business in South America is of no large proportions and we are not represented there. A physician in Buenos Aires, having access to the second edition of this book, and knowing that the formula consisted of an apparently simple mixture of "Adrenal and Pituitary glands (total) aa gr. ½, Ovarian substance gr. 1, Pancreas gland (total) gr. 3," (see page 57), thought he could very conveniently secure these products locally and compound a formula very closely similar to mine, but "the patient did not seem to do as well on this formula, in fact, it must have been quite different from the preparation she had been taking previously"; indicating to my mind that there is perhaps indeed an advantage in going to the expense and trouble to which we go to prepare the very best preparations in our special line that it is possible for us to produce.

The Sanitablet, therefore, prevents deterioration, favors convenience and obviates substitution and imposition on the doctor, the patient and on me.

Favorably Accepted. The reception of this innovation in packing has been very encouraging and has elicited numerous favorable comments. As was to be expected, some physicians have felt that it was unwise and, as one expressed it, that "the new form does not look so professional as the capsule". I have also heard that some physicians evidently have been giving the impression—quite properly, perhaps—that the particular products they were prescribing were made up for each particular patient, and now this fiction cannot be maintained. This, of course, is to be regretted. However, I cannot avoid the conclusion that the Sanitape idea has revolutionized the possibilities of our work and has obviated entirely the three chief obstacles already mentioned with which we have had to contend.

(For some time, at least, we shall continue to supply directly from this office any of our formulas in gelatine capsules; and where comparatively small amounts or special formulas not regularly listed are desired, naturally these will be put up in the same "No. One" gelatine capsules as previously.)

4. OUR ETHICAL STATUS

From the inception of my work I have attempted to adhere as closely as possible to the standards of ethics accepted by the majority of the medical profession. We have had no trade names, and every effort has been made to explain our work and pass on information on the subject as a whole to the profession. We make no secret remedies, and have opened to the profession our complete formulas. There are no indications on the labels. There is no promotion literature in the packages. Every effort has been made to conserve the professional and ethical aspects of both medicine and pharmacy.

Technical Correspondence. Quite a large correspondence of a technical nature comes to my desk and to my medical assistants—for there is indeed much more along this line than I can possibly attend to alone. Such correspondence is welcome, but we refuse to communicate with the laity. It is impossible to practice medicine by correspondence and accurately to determine conditions as they may be at a distance. It is a common thing, however, to be able to gather sufficient information from a letter written by a physician which embodies the essential, clinical points, and with these in mind to be able to make recommendations intelligently *to the physician* to aid in determining the endocrine aspects of the case in question. On the other hand the patients themselves cannot appreciate the technical aspects of what we are doing and it is absolutely necessary to deny them the opportunity of getting in touch with us directly.

Occasionally a layman writes to this office stating that he is doing so on the recommendation of a certain physician whose name is given. Under such circumstances our policy is to acknowledge the letter, give such suggestions as may occur to us, and at the same time communicate with the physician whose name is mentioned, enclosing a carbon copy of the letter to the patient. Frequently a patient writes to us, prompted by results that have been secured by some remote physician in the case of a friend, and under such circumstances we have to insist that our dealings be through some physician in their own town who may be acquainted with our work or, rarely, it may be necessary to acquaint someone with our work in order to enable us to adhere to our rule and at the same time try to help the patient who is writing to us.

Criticism Regarding Advertising. Personally, I do not know how to adhere more thoroughly to the fundamental principles of decency in both professional work and in business and, in spite of this, certain self-constituted judges of both the advances in medicine and of the ethical status of the physician insist that I am an "advertiser"—despite the fact that our advertising never reaches the laity, with our consent, and that we are only attempting to direct the attention *of the profession* to the immense possibilities in the line of work which interests us so much, which in many thousands of instances are being passed over by those physicians. Fortunately many hundreds are appreciating our efforts.

It is impossible to satisfy everybody and the best that I can do is, while adhering strictly to my own ideals of right, to serve as best I may the majority—those who have an open mind and are willing to put these ideas and the products into which they are materialized to the only reasonable test—"the test of results". After all, Crile was right when he referred to "the crucible of the clinic" as the only method of testing the inherent value of a remedy.

5. BRANCH OFFICES

To facilitate distribution of the products of The Harrower Laboratory seven branch offices are maintained in different parts of the United States. With the exception of the New York office, which is combined with that of our sole distributors for New York, New England and New Jersey—Messrs. Morgenstern & Co.—all of these branches are our own branches, manned by our own employees.

Each office carries a full supply of our literature and products and it will be to the advantage of the profession, and the drug trade, to deal with the nearest office. (Letters requesing technical or medical information necessarily must be sent direct to the Home Office at Glendale.) The addresses are as follows: (In each instance address The Harrower Laboratory.)

New York City	31 Park Place	Barclay	9032
Chicago, Ill.	186 N. La Salle St.	Main	1691
Baltimore, Md.	4 East Redwood St.	Plaza	3087
Kansas City, Mo.	711-12 K. C. Life Bldg.	Main	2831
Denver, Colo.	Central Savings Bank Bldg.	Champa	6190
Portland, Ore.	607 Pittock Blk.	Bdwy.	1640
Dallas, Texas	1805½ Commerce St.	Y-	1894

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